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<p>(54) Title: RIFAMYCIN BIOSYNTHESIS GENE CLUSTER</p> <p>(57) Abstract</p> <p>The present invention primarily relates to a DNA fragment which is obtainable from the gene cluster responsible for rifamycin biosynthesis within the genome of <i>Amycolatopsis mediterranei</i>, and comprises at least one gene or a part of a gene which codes for a polypeptide which is directly or indirectly involved in the biosynthesis of rifamycin, and to a method for preparing said DNA fragment. The present invention furthermore relates to recombinant DNA molecules which comprise one of the DNA fragments according to the invention, and to the plasmids and vectors derived therefrom. Host organisms transformed with said plasmid or vector DNA are likewise embraced.</p>		

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Rifamycin biosynthesis gene cluster

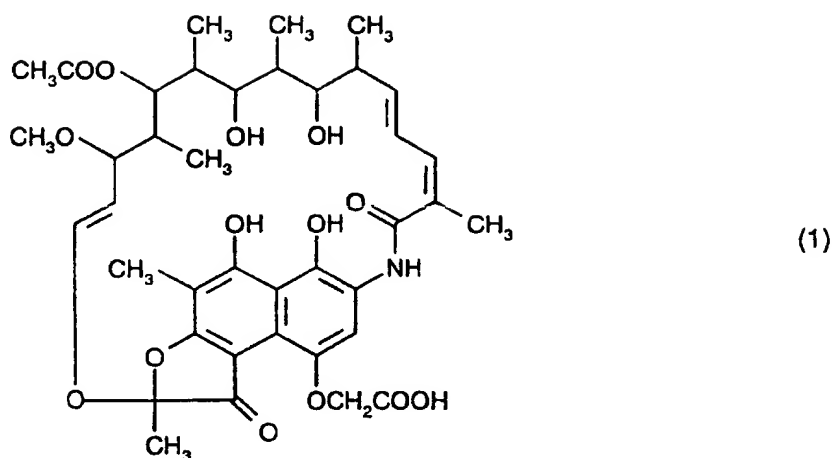
Rifamycins form an important group of macrocyclic antibiotics (Wehrli, Topics in Current Chemistry (1971), 72, 21-49). They consist of a naphthoquinone chromophore which is spanned by a long aliphatic bridge. Rifamycins belong to the class of ansamycin antibiotics which are produced by several Gram-positive soil bacteria of the actinomycetes group and a few plants.

Ansamycins are characterized by a flat aromatic nucleus spanned by a long aliphatic bridge joining opposite positions of the nucleus. Two different groups of ansamycins can be distinguished by the structure of the aromatic nucleus. One group has a naphthoquinoid chromophore, with the typical representatives being rifamycin, streptovaricin, tolypomycin and naphthomycin. The second group, which has a benzoquinoid chromophore, is characterized by geldanamycin, maytansines and ansamitocines (Ghisalba et al., Biotechnology of Industrial Antibiotics Vandamme E. J. Ed., Decker Inc. New York, (1984) 281-327). In contrast to antibiotics of the macrolide type, the ansamycins contain in the aliphatic ring system not a lactone linkage but an amide linkage which forms the connection to the chromophore.

The discovery of the rifamycins produced by the microorganism *Streptomyces mediterranei* (as the organism was called at that time, see below) was described for the first time in 1959 (Sensi et al., Farmaco Ed. Sci. (1959) 14, 146-147). Extraction with ethyl acetate of the acidified cultures of *Streptomyces mediterranei* resulted in isolation of a mixture of antibiologically active components, the rifamycins A, B, C, D and E. Rifamycin B, the most stable component, was separated from the other components and isolated on the basis of its strongly acidic properties and ease of salt formation.

Rifamycin B has the structure of the formula (1)

- 2 -



Rifamycin B is the main component of the fermentation when barbiturate is added to the fermentation medium and/or improved producer mutants of *Streptomyces mediterranei* are used.

The rifamycin producer strain was originally classified as *Streptomyces mediterranei* (Sensi et al., Farmaco Ed. Sci. (1959) 14, 146-147). Analysis of the cell wall of *Streptomyces mediterranei* by Thiemann et al. later revealed that this strain has a cell wall typical of *Nocardia*, and the strain was reclassified as *Nocardia mediterranei* (Thieman et al. Arch. Microbiol. (1969), 67 147-151). *Nocardia mediterranei* has been reclassified again on the basis of more recent accurate morphological and biochemical criteria. Based on the exact composition of the cell wall, the absence of mycolic acid and the insensitivity to *Nocardia* and *Rhodococcus* phages, the strain has been assigned to the new genus *Amycolatopsis* as *Amycolatopsis mediterranei* (Lechevalier et al., Int. J. Syst. Bacteriol. (1986), 36, 29).

Rifamycins have a strong antibiotic activity mainly against Gram-positive bacteria such as mycobacteria, neisserias and staphylococci. The bactericidal effect of rifamycins derives from specific inhibition of the bacterial DNA-dependent RNA polymerase, which interrupts RNA biosynthesis (Wehrli and Staehelin, Bacteriol. Rev. (1971), 35, 290-309). The semisynthetic rifamycin B derivative rifampin (rifampicin) is widely used clinically as antibiotic against the agent causing tuberculosis, *Mycobacterium tuberculosis*.

The naphthoquinoid ansamycins of the streptovaricin and tolypomycin group show, like rifamycin, an antibacterial effect by inhibiting bacterial RNA polymerase. By contrast, naphthomycin has an antibacterial effect without inhibiting bacterial RNA polymerase. The

benzoquinoid ansamycins show no inhibition of bacterial RNA polymerase, and they therefore have only relatively weak antibacterial activity, if any. On the other hand, some representatives of this class of substances have an effect on eukaryotic cells. Thus, antifungal, antiprotozoal and antitumour properties have been described for geldanamycin. On the other hand, antimitotic (antitubilin), antileukaemic and antitumour properties are ascribed to the maytansines. Some rifamycins also show antitumour and antiviral activity, but only at high concentrations. This biological effect thus appears to be nonspecific.

Despite the great structural variety of the ansamycins, their biosynthesis appears to take place by a metabolic pathway which contains many common elements (Ghisalba et al. *Biotechnology of Industrial Antibiotics* Vandamme E. J. Ed., Decker Inc. New York, (1984) 281-327). The aromatic nucleus for all ansamycins is probably built up starting from 3-amino-5-hydroxybenzoic acid. Starting from this molecule, which is presumably activated as coenzyme A, the entire aliphatic bridge is synthesized by a multifunctional polyketide synthase. The length of the bridge and the processing of the keto groups, which are initially formed by the condensation steps, are controlled by the polyketide synthase. To build up the complete aliphatic bridge for rifamycins, 10 condensation steps, 2 with acetate and 8 with propionate as building blocks, are necessary. The sequence of these individual condensation steps is likewise determined by the polyketide synthase. Structural comparisons and studies with incorporation of radioactive acetate and propionate have shown that the sequence of acetate and propionate incorporation for the various ansamycins takes place in accordance with a scheme which appears to be identical or very similar in the first condensation steps. Thus, from a common synthesis scheme of the ansamycin polyketide synthases (the rifamycin synthesis scheme), the syntheses of the various ansamycins sooner or later branch off, in accordance with their structural difference from the rifamycin structure, into side branches of the synthesis (Ghisalba et al., *Biotechnology of Industrial Antibiotics* Vandamme E. J. Ed., Decker Inc. New York, (1984) 281-327).

Because of the great structural variety of the rifamycins and their specific and interesting biological effect, there is great interest in understanding the genetic basis of their synthesis in order to create the possibility of specifically influencing it. This is particularly desirable because, as explained above, there is much in common between the synthesis of rifamycins and that of other ansamycins. This similarity in the biosynthesis, which probably derives from a common evolutionary origin of this metabolic pathway, naturally has a genetic basis.

The genetic basis of secondary metabolite biosynthesis essentially exists in the genes which code for the individual biosynthetic enzymes, and in the regulatory elements which control the expression of the biosynthesis genes. The secondary metabolite synthesis genes of actinomycetes have hitherto been found as clusters of adjacent genes in all the systems investigated. The size of such antibiotic gene clusters extends from about 10 kilobases (kb) up to more than 100 kb. The clusters often contain specific regulator genes and genes for resistance of the producer organism to its own antibiotic (Chater, Ciba Found. Symp. (1992), 171, 144-162).

The invention described herein has now succeeded, by identifying and cloning genes of rifamycin biosynthesis, in creating the genetic basis for synthesizing by genetic methods rifamycin analogues or novel ansamycins which combine structural elements from rifamycin with other ansamycins. This also creates the basis for preparing novel collections of substances based on the rifamycin biosynthesis gene cluster by combinatorial biosynthesis.

It was possible in a first step to identify and clone a DNA fragment from the genome of *A. mediterranei*, which shows homology with known polyketides synthase genes. After obtaining the sequence information from this DNA fragment which confirmed a typical sequence for polyketide synthases it was possible to screen a cosmid library of *A. mediterranei* with specific DNA probes derived from this fragment in a screening program for further DNA fragments which are involved in the rifamycin gene cluster. As a result, the complete rifamycin polyketide synthase gene cluster was identified and subjected to sequence determination (see SEQ ID NO 3). The gene cluster comprises six open reading frames, which are referred to hereinafter as ORF A, B, C, D, E and F and which code for the proteins and polypeptides depicted in SEQ ID NOS 4 to 9.

The gene cluster isolated and characterized in this way represents the basis, for example, for targeted optimization of the production of rifamycin, ansamycins or analogues thereof. Examples of techniques and possible areas of application available in this connection are as follows:

- Overexpression of individual genes in producer strains with plasmid vectors or by incorporation into the chromosome.
- Study of the expression and transcriptional regulation of the gene cluster during fermentation with various producer strains and optimization thereof through physiological parameters and appropriate fermentation conditions.

- Identification of regulatory genes and of the DNA binding sites of the corresponding regulatory proteins in the gene cluster. Characterization of the effect of these regulatory elements on the production of rifamycins or ansamycins; and influencing them by specific mutation in these genes or the DNA binding sites.
- Duplication of the complete gene cluster or parts thereof in producer strains.

Besides these applications of the gene cluster to improve production by fermentation as described above, it can likewise be employed for the biosynthetic preparation of novel rifamycin analogues or novel ansamycins or ansamycin-like compounds in which the aliphatic bridge is connected at only one end to the aromatic nucleus. The following possibilities come into consideration here, for example:

- Inactivation of individual steps in the biosynthesis, for example by gene disruption.
- Mutation of individual steps in the biosynthesis, for example by gene replacement.
- Use of the cluster or fragments thereof as DNA probe in order to isolate other natural microorganisms which produce metabolites similar to rifamycin or ansamycins.
- Exchange of individual elements in this gene cluster by those from other gene clusters.
- Use of modified polyketide synthases for setting up libraries of various rifamycin analogues or ansamycins, which are then tested for their activity (Jackie & Khosla, Chemistry & Biology, (1995), 2, 355-362).
- Construction of mutated actinomycetes strains from which the natural rifamycin or ansamycin biosynthesis gene cluster in the chromosome has been partly or completely deleted, and can thus be used for expressing genetically modified gene clusters.
- Exchange of individual elements within the gene cluster.

Detailed description of the invention

The invention relates to a DNA fragment from the genome of *Amycolatopsis mediterranei*, which comprises a DNA region which is involved directly or indirectly in the gene cluster responsible for rifamycin synthesis; and the adjacent DNA regions; and functional constituents or domains thereof.

The DNA fragments according to the invention may moreover comprise regulatory sequences such as promoters, repressor or activator binding sites, repressor or activator genes, terminators; or structural genes. Likewise part of the invention are any combinations of these DNA fragments with one another or with other DNA fragments, for example combinations of promoters, repressor or activator binding sites and/or repressor or activator genes from an ansamycin gene cluster, in particular from the rifamycin gene cluster, with

foreign structural genes or combinations of structural genes from the ansamycin gene cluster, especially the rifamycin gene cluster, with foreign promoters; and combinations of structural genes with one another or with gene fragments which code for enzymatically active domains and are from various ansamycin biosynthesis systems. Foreign structural genes, and foreign gene fragments coding for enzymatically active domains, code, for example, for proteins involved in the biosynthesis of other ansamycins.

A preferred DNA fragment is one directly or indirectly involved in the gene cluster responsible for rifamycin synthesis.

The gene cluster or DNA region described above contains, for example, the genes which code for the individual enzymes involved in the biosynthesis of ansamycins and, in particular, of rifamycin, and the regulatory elements which control the expression of the biosynthesis genes. The size of such antibiotic gene clusters extends from about 10 kilobases (kb) up to over 100 kb. The gene clusters normally comprise specific regulatory genes and genes for resistance of the producer organism to its own antibiotic. Examples of what is meant by enzymes or enzymatically active domains involved in this biosynthesis are those necessary for synthesizing, starting from 3-amino-5-hydroxybenzoic acid, the ansamycins such as rifamycin, for example polyketide synthases, acyltransferases, dehydratases, ketoreductases, acyl carrier proteins or ketoacyl synthases.

Thus, the complete sequence of the gene cluster shown in SEQ ID NO 3, as well as DNA fragments which comprise sequence portions which code for a polyketide synthase or an enzymatically active domain thereof, are particularly preferred. Examples of such preferred DNA fragments are, for example, those which code for one or more of the proteins and polypeptides depicted in SEQ ID NOS 4, 5, 6, 7, 8 and 9, or functional derivatives thereof, also including partial sequences thereof which comprise, for example, 15 or more consecutive nucleotides. Other preferred embodiments relate to DNA regions of the gene cluster according to the invention or fragments thereof, like those present in the deposited clones pNE95, pRi44-2 and pNE112, or derived therefrom. Further preferred DNA fragments are those comprising sequence portions which display homologies with the sequences comprised by the clones pNE95, pRi44-2 and/or pNE112 or with SEQ ID NOS 1 and/or 3, and therefore can be used as hybridization probe within a genomic gene bank of an ansamycin-, in particular, rifamycin-producing organism for finding constituents

of the corresponding gene cluster. The DNA fragment may moreover, for example, comprise exclusively genomic DNA. A particularly preferred DNA fragment is one which comprises the nucleotide sequence depicted in SEQ ID NO 1 or 3, or partial sequences thereof, which, by reason of homologies, can be regarded as structural or functional equivalent to said sequence or partial sequence therefrom, and which therefore are able to hybridize with this sequence.

The DNA fragments according to the invention comprise, for example, sequence portions which comprise homologies with the above-described enzymes, enzyme domains or fragments thereof.

The term homologies and structural and/or functional equivalents refers primarily to DNA and amino acid sequences with few or minimal differences between the relevant sequences. These differences may have very diverse causes. Thus, for example, this may entail mutations or strain-specific differences which occur naturally or are artificially induced. Or the differences observed from the initial sequence are derived from a targeted modification, which can be introduced, for example, during a chemical synthesis.

Functional differences can be regarded as minimal if, for example, the nucleotide sequence coding for a polypeptide, or a protein sequence has essentially the same characteristic properties as the initial sequence, whether in respect of enzymatic activity, immunological reactivity or, in the case of a nucleotide sequence, gene regulation.

Structural differences can be regarded as minimal as long as there is a significant overlap or similarity between the various sequences, or they have at least similar physical properties. The latter include, for example, the electrophoretic mobility, chromatographic similarities, sedimentation coefficients, spectrophotometric properties etc.

In the case of nucleotide sequences, the agreement should be at least 70%, but preferably 80% and very particularly preferably 90% or more. In the case of the amino acid sequence, the corresponding figures are at least 50%, but preferably 60% and particularly preferably 70%. 90% agreement is very particularly preferred.

The invention furthermore relates to a method for identifying, isolating and cloning one of the DNA fragments described above. A preferred method comprises, for example, the following steps:

- a) setting up of a genomic gene bank,
- b) screening of this gene bank with the assistance of the DNA sequences according to the invention, and
- c) isolation of the clones identified as positive.

A general method for identifying DNA fragments involved in the biosynthesis of ansamycins comprises, for example, the following steps

- 1) Cloning of a DNA fragment which shows homology with known polyketide synthase genes.
 - a) The presence of DNA fragments having homology with the polyketide synthase genes according to the invention is detected in the strains of the microorganism to be investigated by a Southern experiment with chromosomal DNA of this strain. The size of such homologous DNA fragments can be determined by digesting the DNA with a suitable restriction enzyme.
 - b) Production of a plasmid gene bank comprising the above digested chromosomal fragments. Normally, individual clones of this gene bank are tested once again for homology with the polyketide synthase genes according to the invention. Clones with recombinant plasmids comprising fragments having homology with the polyketide probe are then normally isolated on the basis of this homology.
- 2) Analysis of the cloned region
 - a) Restriction analysis of the isolated recombinant plasmids and checking of the identity of these cloned fragments with one another.
 - b) By a chromosomal Southern with DNA of the original microorganism and the isolated DNA fragment as probe it can be demonstrated that the cloned fragment is an original chromosomal DNA fragment from the original microorganism.
 - c) It is possible as an option to demonstrate a significant homology of the cloned DNA fragment with chromosomal DNA from other ansamycin producers (streptovaricin, tolypomycin, geldanamycin, ansamitocin). This would confirm that the cloned DNA is typical of gene clusters of ansamycin biosynthesis and thus also of rifamycin biosynthesis.

- d) DNA sequencing of an internal restriction fragment and demonstration by comparative sequence analysis that the cloned region is a typical DNA sequence of polyketide synthases, coding for the biosynthesis of polyketide antibiotics from actinomycetes.
- 3) Isolation and characterization of adjacent DNA regions
- a) Construction of a cosmid gene bank from the original microorganism and analysis thereof for homology with the isolated fragments. Isolation of cosmids having homology with this fragment.
 - b) Demonstration by restriction analysis that the isolated cosmid clones comprise a DNA region of the original microorganism which overlaps with the original fragment.

As described above, the first step in the isolation of the DNA fragments according to the invention is normally the setting up of genomic gene banks from the organism of interest, which synthesize the required ansamycin, especially rifamycin.

Genomic DNA can be obtained from a host organism in various ways, for example by extraction from the nuclear fraction and purification of the extracted DNA by known methods.

The fragmentation, which is necessary for setting up a representative gene bank, of the genomic DNA to be cloned to a size which is suitable for insertion into a cloning vector can take place either by mechanical shearing or else, preferably, by cutting with suitable restriction enzymes.

Suitable cloning vectors, which are already in routine use for producing genomic gene libraries, comprise, for example, cosmid vectors, plasmid vectors or phage vectors.

It is then possible in a screening program to obtain suitable clones which comprise the required gene(s) or gene fragment(s) from the gene libraries produced in this way.

One possibility for identifying the required DNA region consists in, for example, using the gene bank described above to transform strains which, because of a blocked synthetic pathway, are unable to produce ansamycins, and identifying those clones which are again able after the transformation to produce ansamycin (revertants). The vectors which lead to revertants comprise a DNA fragment which is required in ansamycin synthesis.

Another possibility for identifying the required DNA region is based, for example, on using suitable probe molecules (DNA probe) which are obtained for example as described above. Various standard methods are available for identifying suitable clones, such as differential colony hybridization or plaque hybridization.

It is possible to use as probe molecule a previously isolated DNA fragment from the same or a structurally related gene or gene cluster which, because of the homologies present, is able to hybridize with the corresponding sequence section within the required gene or gene cluster to be identified. Preferably used as probe molecule for the purpose of the present invention is a DNA fragment obtainable from a gene or a DNA sequence involved in the synthesis of polyketides such as ansamycins or soraphens.

If the nucleotide sequence of the gene to be isolated, or at least parts of this sequence, are known, it is possible in an alternative embodiment to use, based on this sequence information, a corresponding synthesized DNA sequence for the hybridizations or PCR amplifications.

In order to facilitate detectability of the required gene or else parts of a required gene, one of the DNA probe molecules described above can be labelled with a suitable, easily detectable group. A detectable group for the purpose of this invention means any material which has a particular, easily identifiable, physical or chemical property.

Particular mention may be made at this point of enzymatically active groups such as enzymes, enzyme substrates, coenzymes and enzyme inhibitors, furthermore fluorescent and luminescent agents, chromophores and radioisotopes such as ^3H , ^{35}S , ^{32}P , ^{125}I and ^{14}C . Easy detectability of these markers is based, on the one hand, on their intrinsic physical properties (for example fluorescent markers, chromophores, radioisotopes) or, on the other hand, on their reaction and binding properties (for example enzymes, substrates, coenzymes, inhibitors). Materials of these types are already widely used in particular in immunoassays and, in most cases, can also be used in the present application.

General methods relating to DNA hybridization are described, for example, by Maniatis T. *et al.*, Molecular Cloning, Cold Spring Harbor Laboratory Press (1982).

Those clones within the previously described gene libraries which are able to hybridize with a probe molecule and which can be identified by one of the abovementioned detection methods can then be further analysed in order to determine the extent and nature of the coding sequence in detail.

An alternative method for identifying cloned genes is based on constructing a gene library consisting of plasmid or expression vectors. This entails, in analogy to the methods described previously, the genomic DNA comprising the required gene being initially isolated and then cloned into a suitable plasmid or expression vector. The gene libraries produced in this way can then be screened by suitable procedures, for example by use of complementation studies, and those clones which comprise the required gene or else at least a part of this gene as insert can be selected.

It is thus possible with the aid of the methods described above to isolate a gene, several genes or a gene cluster which code for one or more particular gene products.

For further characterization, the DNA sequences purified and isolated in the manner described above are subjected to restriction analysis and sequence analysis.

For sequence analysis, the previously isolated DNA fragments are first fragmented using suitable restriction enzymes, and then cloned into suitable cloning vectors. In order to avoid mistakes in the sequencing, it is advantageous to sequence both DNA strands completely.

Various alternatives are available for analysing the cloned DNA fragment in respect of its function within ansamycin biosynthesis.

Thus, for example, it is possible in complementation experiments with defective mutants not only to establish involvement in principle of a gene or gene fragment in secondary metabolite biosynthesis, but also to verify specifically the synthetic step in which said DNA fragment is involved.

In an alternative type of analysis, evidence is obtained in exactly the opposite way. Transfer of plasmids which comprise DNA sections which have homologies with appropriate sections

on the genome results in integration of said homologous DNA sections via homologous recombination. If, as in the present case, the homologous DNA section is a region within an open reading frame of the gene cluster, plasmid integration results in inactivation of this gene by so-called gene disruption and, consequently, in an interruption in secondary metabolite production. It is assumed according to current knowledge that a homologous region which comprises at least 100 bp, but preferably more than 1000 bp, is sufficient to bring about the required recombination event.

However, a homologous region which extends over a range of from 0.3 to 4 kb, but in particular over a range of from 1 to 3 kb, is preferred.

To prepare suitable plasmids which have sufficient homology for integration via homologous recombination there is preferably provision of a subcloning step in which the previously isolated DNA is digested, and fragments of suitable size are isolated and subsequently cloned into a suitable plasmid. Examples of suitable plasmids are the plasmids generally used for genetic manipulations in streptomycetes or *E. coli*.

It is possible in principle to use for the preparation and multiplication of the previously described constructs all conventional cloning vectors such as plasmid or bacteriophage vectors as long as they have replication and control sequences derived from species compatible with the host cell.

The cloning vector usually has an origin of replication plus specific genes which result in phenotypical selection features in the transformed host cell, in particular resistances to antibiotics. The transformed vectors can be selected on the basis of these phenotypical markers after transformation in a host cell.

Selectable phenotypical markers which can be used for the purpose of this invention comprise, for example, without this representing a limitation of the subject-matter of the invention, resistances to thiostrepton, ampicillin, tetracycline, chloramphenicol, hygromycin, G418, kanamycin, neomycin and bleomycin. Another selectable marker can be, for example, prototrophy for particular amino acids.

Mainly preferred for the purpose of the present invention are streptomycetes and *E. coli* plasmids, for example the plasmids used for the purpose of the present invention.

Host cells primarily suitable for the previously described cloning for the purpose of this invention are prokaryotes, including bacterial hosts such as streptomycetes, actinomycetes, *E. coli* or pseudomonads.

E. coli hosts are particularly preferred, for example the *E. coli* strain HB101 or X-1 blue MR[®](Stratagene) or streptomycetes such as the plasmid-free strains of *Streptomyces lividans* TK23 and TK24.

Competent cells of the *E. coli* strain HB101 are produced by the methods normally used for transforming *E. coli*. The transformation method of Hopwood *et al.* (Genetic manipulation of streptomycetes a laboratory manual. The John Innes Foundation, Norwich (1985)) is normally used for streptomycetes.

After transformation and subsequent incubation on a suitable medium, the resulting colonies are subjected to a differential screening by plating out on selective media. It is then possible to isolate the appropriate plasmid DNA from those colonies which comprise plasmids with DNA fragments cloned in.

The DNA fragment according to the invention, which comprises a DNA region which is involved directly or indirectly in the biosynthesis of ansamycin and can be obtained in the previously described manner from the ansamycin biosynthesis gene cluster, can also be used as starter clone for identifying and isolating other adjacent DNA regions overlapping therewith from said gene cluster.

This can be achieved, for example, by carrying out a so-called chromosome walking within a gene library consisting of DNA fragments with mutually overlapping DNA regions, using the previously isolated DNA fragment or else, in particular, the sequences located at its 5' and 3' margins. The procedures for chromosome walking are known to the person skilled in this art. Details can be found, for example, in the publications by Smith *et al.* (Methods

Enzymol (1987), 151, 461-489) and Wahl *et al.* (Proc Natl. Acad. Sci, USA (1987), 84, 2160-2164).

The prerequisite for chromosome walking is the presence of clones having coherent DNA fragments which are as long as possible and mutually overlap within a gene library, and a suitable starter clone which comprises a fragment which is located in the vicinity or else, preferably, within the region to be analysed. If the exact location of the starter clone is unknown, the walking is preferably carried out in both directions.

The actual walking step starts by using the identified and isolated starter clone as probe in one of the previously described hybridization reactions in order to detect adjacent clones which have regions overlapping with the starter clone. It is possible by hybridization analysis to establish which fragment projects furthest over the overlapping region. This is then used as starting clone for the 2nd walking step, in which case there is establishment of the fragment which overlaps with said 2nd clone in the same direction. Continuous progression in this manner on the chromosome results in a collection of overlapping DNA clones which cover a large DNA region. These can then, where appropriate after one or more subcloning steps, be ligated together by known methods to give a fragment which comprises parts or else, preferably all of the constituents essential for ansamycin biosynthesis.

The hybridization reaction to establish clones with overlapping marginal regions preferably makes use not of the very large and unwieldy complete fragment but, in its place, a partial fragment from the left or right marginal region, which can be obtained by a subcloning step. Because of the smaller size of said partial fragment, the hybridization reaction results in fewer positive hybridization signals, so that the analytical effort is distinctly less than on use of the complete fragment. It is furthermore advisable to characterize the partial fragment in detail in order to preclude its comprising larger amounts of repetitive sequences, which may be distributed over the entire genome and thus would greatly impede a targeted sequence of walking steps.

Since the gene cluster responsible for ansamycin biosynthesis covers a relatively large region of the genome, it may also be advantageous to carry out a so-called large-step walking or cosmid walking. It is possible in these cases, by using cosmid vectors which

permit the cloning of very large DNA fragments, to cover a very large DNA region, which may comprise up to 42 kb, in a single walking step.

In one possible embodiment of the present invention, for example, to construct a cosmid gene bank from streptomycetes or actinomycetes, complete DNA is isolated with the size of the DNA fragments being of the order of about 100 kb, and is subsequently partially digested with suitable restriction endonucleases.

The digested DNA is then extracted in a conventional way in order to remove endonuclease which is still present, and is precipitated and finally concentrated. The resulting fragment concentrate is then fractionated, for example by density gradient centrifugation, in accordance with the size of the individual fragments. After the fractions obtainable in this way have been dialysed they can be analysed on an agarose gel. The fractions which contain fragments of suitable size are pooled and concentrated for further processing. Fragments to be regarded as particularly suitable for the purpose of this invention have a size of the order of 30 kb to 42 kb, but preferably of 35 kb to 40 kb.

In parallel with the fragmentation described above, or later, for example a suitable cosmid vector pWE15[®] (Stratagene) is completely digested with a suitable restriction enzyme, for example BamHI, for the subsequent ligase reaction.

Ligation of the cosmid DNA to the streptomycetes or actinomycetes fragments which have been fractionated according to their size can be carried out using a T4 DNA ligase. The ligation mixture obtainable in this way is, after a sufficient incubation time, packaged into λ phages by generally known methods.

The resulting phage particles are then used to infect a suitable host strain. A *recA*⁻ *E. coli* strain is preferred, such as *E. coli* HB101 or X-1 Blue[®] (Stratagene). Selection of transfected clones and isolation of the plasmid DNA can be carried out by generally known methods.

The screening of the gene bank for DNA fragments which are involved in ansamycin biosynthesis is carried out, for example, using a specific hybridization probe which is assumed (for example on the basis of DNA sequence or DNA homology or

complementation tests or gene disruption or the function thereof in other organisms) to comprise DNA regions from the 'ansamycin gene cluster'.

A plasmid which comprises an additional fragment of the required size or has been identified on the basis of hybridizations can then be isolated from the gel in the previously described manner. The identity of this additional fragment with the required fragment of the previously selected cosmid can then be confirmed by Southern transfer and hybridization.

Function analysis of the DNA fragments isolated in this way can be carried out in a gene disruption experiment as described above.

Another possible use of the DNA fragments according to the invention is to modify or inactivate enzymes or domains involved in ansamycin and, in particular, rifamycin biosynthesis, or to synthesize oligonucleotides which are then in turn used for finding homologous sequences in PCR amplification.

Besides the DNA fragments according to the invention as such, also claimed are their use firstly for producing rifamycin, rifamycin analogues or precursors thereof, and for the biosynthetic production of novel ansamycins or of precursors thereof. Included in this connection are those molecules in which the aliphatic bridge is connected only at one end to the aromatic nucleus.

The DNA fragments according to the invention permit, for example, by combination with DNA fragments from other biosynthetic pathways or by inactivation or modification thereof, the biosynthesis of novel hybrid compounds, in particular of novel ansamycins or rifamycin analogues. The steps necessary for this are generally known and are described, for example, in Hopwood, *Current Opinion in Biotechnol.* (1993), **4**, 531-537.

The invention furthermore relates to the use of the DNA fragments according to the invention for carrying out the novel technology of combinatorial biosynthesis for the biosynthetic production of libraries of polyketide synthases based on the rifamycin and ansamycin biosynthesis genes. If, for example, several sets of modifications are produced, it is possible in this way to produce, by means of biosyntheses, a library of polyketides, for example ansamycins or rifamycin analogues, which then needs to be tested only for the

activity of the compounds produced in this way. The steps necessary for this are generally known and are described, for example, in Tsoi and Khosla, Chemistry & Biology (1995), 2, 355-362 and WO-9508548.

Besides the DNA fragment as such, also claimed is its use for the genetic construction of mutated actinomycetes strains from which the natural rifamycin or ansamycin biosynthesis gene cluster in the chromosome has been partly or completely deleted, and which can thus be used for expressing genetically modified ansamycin or rifamycin biosynthesis gene clusters.

The invention furthermore relates to a hybrid vector which comprises at least one DNA fragment according to the invention, for example a promoter, a repressor or activator binding site, a repressor or activator gene, a structural gene, a terminator or a functional part thereof. The hybrid vector comprises, for example, an expression cassette which comprises a DNA fragment according to the invention which is able to express one or more proteins involved in ansamycin biosynthesis and, in particular in rifamycin biosynthesis, or a functional fragment thereof. The invention likewise relates to a host organism which comprises the hybrid vector described above.

Suitable vectors representing the starting point of the hybrid vectors according to the invention, and suitable host organisms such as bacteria or yeast cells are generally known.

The host organism can be transformed by generally customary methods such as by means of protoplasts, Ca^{2+} , Cs^+ , polyethylene glycol, electroporation, viruses, lipid vesicles or a particle gun. The DNA fragments according to the invention may then be present both as extrachromosomal constituents in the host organism and integrated via suitable sequence sections into the chromosome of the host organism.

The invention likewise relates to polyketide synthases which comprise the DNA fragments according to the invention, in particular those from *Amycolatopsis mediterranei* which are involved directly or indirectly in rifamycin synthesis, and functional constituents thereof, for example enzymatically active domains.

The invention furthermore relates to a hybridization probe comprising a DNA fragment according to the invention, and to the use thereof, in particular for identifying DNA fragments involved in the biosynthesis of ansamycins.

In order to obtain unambiguous signals in the hybridization, DNA bound to the filter (for example made of nylon or nitrocellulose) is normally washed at 55-65°C in 0.2 × SSC (1 × SSC = 0.15 M sodium chloride, 15 mM sodium citrate).

Examples

General

General molecular genetic techniques such as DNA isolation and purification, restriction digestion of DNA, agarose gel electrophoresis of DNA, ligation of restriction fragments, cultivation and transformation of *E. coli*, plasmid isolation from *E. coli*, are carried out as described in Maniatis et al., Molecular Cloning: A laboratory manual, 1st Edit. Cold Spring Harbor Laboratory Press, Cold Spring Harbor NY (1982).

Culture conditions and molecular genetic techniques with *A. mediterranei* and other *actinomycetes* are as described by Hopwood *et al.* (Genetic manipulation of streptomyces a laboratory manual, The John Innes Foundation, Norwich, 1985). All liquid cultures of *A. mediterranei* and other *actinomycetes* are carried out in Erlenmeyer flasks at 28°C on a shaker at 250 rpm.

Nutrient media used:

LB Maniatis et al., Molecular Cloning: A laboratory manual, 1st Edit. Cold Spring Harbor Laboratory Press, Cold Spring Harbor NY (1982)

NL148 Schupp + Divers FEMS Microbiology Lett. **36**, 159-162 (1986) (NL148 = NL148G without glycine)

R2YE Hopwood *et al.* (Genetic manipulation of streptomyces a laboratory manual. The John Innes Foundation, Norwich, 1985)

TB : 12 g/l Bacto tryptone
24 g/l Bacto yeast extract
4 ml/l glycerol

Example 1: Detection of chromosomal DNA fragments from *A. mediterranei* having homology with polyketide synthase genes of other bacteria

To obtain genomic DNA from *A. mediterranei*, cells of the strain *A. mediterranei* wt3136 (= LBGA 3136, ETH collection of strains) are cultivated in NL148 medium for 48 hours. 1 ml of this culture is then transferred into 50 ml of NL148 medium (+ 2.5 g/l glycine) in a 200 ml Erlenmeyer flask, and the culture is incubated for 48 h. The cells are removed from the medium by centrifugation at 3000 g for 10 min. and are resuspended in 5 ml of SET (75 mM NaCl, 25 mM EDTA, 20 mM Tris, pH 7.5). High molecular weight DNA is extracted by the method of Pospiech and Neumann (Trends in Genetics (1995), 11, 217-218).

In order to detect, by a Southern blot, individual fragments from the isolated *A. mediterranei* DNA which have homology with polyketide synthase genes, a radioactive DNA probe is prepared from a known polyketide synthase gene cluster. To do this, the PvuI fragment 3.8 kb in size is isolated from the recombinant plasmid p98/1 (Schupp et al. J. of Bacteriol. (1995), 177, 3673-3679), which comprises a DNA region, about 32 kb in size, from the polyketide synthase for the antibiotic soraphen A. About 0.5 µg of the isolated 3.8 kb PvuI DNA fragment is radiolabelled with ³²P-d-CTP by the nick translation system from Gibco/BRL (Basle) in accordance with the manufacturer's instructions.

For the Southern blot, about 2 µg of the genomic DNA isolated above from *A. mediterranei* are completely digested with the restriction enzyme BglII (Böhringer, Mannheim), and the resulting fragments are fractionated on a 0.8% agarose gel. A Southern blot with this agarose gel and the DNA probe isolated above (3.8 kb PvuI fragment) detects a DNA BglII-cut fragment which is about 13 kb in size from the genomic DNA of *A. mediterranei*, and which has homology with the DNA probe used. It can be concluded on the basis of this homology that the detected DNA fragment from *A. mediterranei* is a genetic region which codes for a polyketide synthase and thus is involved in the synthesis of a polyketide antibiotic.

Example 2: Production of a specific recombinant plasmid collection comprising BglII-digested chromosomal fragments from *A. mediterranei* 12-16 kb in size

The *E. coli* positive selection vector pIJ4642 (derivative of pIJ666, Kieser & Melton, Gene (1988), 65, 83-91) developed at the John Innes Centre (Norwich, UK) is used to produce the plasmid gene bank. This plasmid is first cut with BamHI, and the two resulting fragments are fractionated on an agarose gel. The smaller of the two fragments is the filler fragment of the vector and the larger is the vector portion which, on self-ligation after deletion of the filler fragment, forms, owing to the flanking fd termination sequences, a perfect palindrome, which means that the plasmid cannot be obtained as such in *E. coli*. This vector portion 3.8 kb in size is isolated from the agarose gel by electroelution as described on page 164-165 of Maniatis et al., Molecular Cloning: A laboratory manual, 1st Edit. Cold Spring Harbor Laboratory Press, Cold Spring Harbor NY (1982).

To prepare the BglII-cut DNA fragments from *A. mediterranei*, the high molecular weight genomic DNA prepared in Example 1 is used. About 10 µg of this DNA are completely digested with the restriction enzyme BglII and subsequently fractionated on a 0.8% agarose gel. DNA fragments with a size of about 12 - 16 kb are cut out of the gel and detached from the gel block by electroelution (see above). About 1 µg of the BglII fragments isolated in this way is ligated to about 0.1 µg of the BamHI portion, isolated above, of the vector pIJ4642. The ligation mixture obtained in this way is then transformed into the *E. coli* strain HB101 (Stratagene). About 150 transformed colonies are selected from the transformation mixture on LB agar with 30 µg per ml chloramphenicol. These colonies contain recombinant plasmids with BglII-cut genomic DNA fragments from *A. mediterranei* in the size range 12 - 16 kb.

Example 3: Cloning and characterization of chromosomal *A. mediterranei* DNA fragments having homology with bacterial polyketide synthase genes

150 of the plasmid clones prepared in Example 2 are analysed by colony hybridization using a nitrocellulose filter (Schleicher & Schuell) as described on pages 318-319 of Maniatis et al., Molecular Cloning: A laboratory manual, 1st Edit. Cold Spring Harbor Laboratory Press, Cold Spring Harbor NY (1982). The DNA probe used is the 3.8 kb PvuI fragment, radiolabelled with ³²P-d-CTP and isolated in Example 1, of the plasmid p98/1. The plasmids are isolated from 5 plasmid clones which show a hybridization signal, and are characterized by two restriction digestions with the enzymes HindIII or KpnI. HindIII cuts

twice in the vector portion of the clones, 0.3 kb to the right and left of the BamHI cleavage site into which the *A. mediterranei* DNA has been integrated. KpnI does not cut in the pIJ 4642 vector portion. This restriction analysis shows that the investigated clones comprise both identical HindIII fragments of about 14 and 3.1 kb and identical KpnI fragments approximately 11.4 kb and 5.7 kb in size. This shows that these clones comprise the same genomic BglII fragment of *A. mediterranei*, and that the latter has a size of about 13 kb. It can additionally be concluded from this restriction analysis that this cloned BglII fragment has no internal HindIII cleavage site, but has 2 KpnI cleavage sites which afford an internal KpnI fragment 5.7 kb in size.

The plasmid DNA of the above 5 clones with identical restriction fragments is further characterized by a Southern blot. For this purpose, the plasmids are cut with HindIII and KpnI, and the DNA probe used is the ³²P-radiolabelled 3.8 kb PvuI fragment of the plasmid p98/1 used above. This experiment confirms that the 5 plasmids contain identical *A. mediterranei* DNA fragments and that these have significant homology with the DNA probe which is characteristic of bacterial polyketide synthase genes. In addition, the Southern blot shows that the internal KpnI fragment 5.7 kb in size likewise has significant homology with the DNA probe used. The plasmid called pRi7-3 is selected from the 5 plasmids for further processing.

To demonstrate that the cloned BglII fragment about 13 kb in size from *A. mediterranei* is an original chromosomal DNA fragment, another Southern blot is carried out. Chromosomal DNA from *A. mediterranei* which has been cut with BglII, KpnI or BamHI is employed in this blot. Two BamHI fragments which are about 1.8 and 1.9 kb in size and are present in the 5.7 kb KpnI fragment of pRi7-3 are used as radiolabelled DNA probe. This experiment confirms that the BglII DNA fragment about 13 kb in size cloned in the recombinant plasmid pRi7-3 is an authentic genomic DNA fragment from *A. mediterranei*. In addition, this experiment confirms that the cloned fragment comprises an internal KpnI fragment 5.7 kb in size and two BamHI fragments about 1.8 and 1.9 kb in size, and that these DNA fragments are likewise authentic genomic DNA fragments from *A. mediterranei*.

Example 4: Demonstration of a significant homology of the cloned genomic 13 kb BglII fragment from *A. mediterranei* with chromosomal DNA from other actinomycetes which produce ansamycins

Demonstration of a significant homology between the cloned chromosomal DNA region of *A. mediterranei* and chromosomal DNA from other ansamycin-producing actinomycetes takes place by a Southern blot experiment. The following ansamycin-producing strains are employed for this purpose (the ansamycins produced by the strains are in parentheses): *Streptomyces spectabilis* (streptovaricins), *Streptomyces tolypophorus* (tolypomycins), *Streptomyces hygroscopicus* (geldanamycins), *Nocardia species* ATCC31281 (ansamitocins). Genomic DNA from these strains is isolated as described for *A. mediterranei* in Example 1 and digested with the restriction enzyme KpnI, and the restriction fragments obtained in this way are fractionated on an agarose gel for the Southern blot. Two BamHI fragments about 1.8 and 1.9 kb in size from *A. mediterranei*, which are used in Example 3 and are isolated from the plasmid pRi7-3, are used as radioactive probe. This experiment shows that these ansamycin-producing strains have a significant DNA homology with the DNA probe used and thus with the cloned chromosomal region of *A. mediterranei*. It is to be observed in this connection that the homology in the case of producers of ansamycins with a naphthoquinoid ring system (streptovaricin, tolypomycin) is greater than in the case of those with a benzoquinoid ring system (geldanamycin, ansamitocin). This result suggests that the cloned chromosomal DNA region from *A. mediterranei* is typical of ansamycin biosynthesis gene clusters and, especially, of gene clusters for ansamycins with naphthoquinoid ring systems, corresponding to the ring system in rifamycins.

Example 5: DNA sequence determination of the KpnI fragment 5.7 kb in size located within the cloned 13 kb BglII fragment

For the sequencing, the 5.7 kb KpnI fragment is isolated from the plasmid pRi7-3 (DSM 11114) (Maniatis et. al. 1992) and subcloned into the KpnI cleavage site of the vector pBRKanf4, which is suitable for the DNA sequencing, affording the plasmids pTS004 and pTS005. The vector pBRKanf4 (derived from pBRKanf1; Bhat, Gene (1993) 134, 83-87) is suitable for introducing sequential deletions of Sau3A fragments in the cloned insert fragment, because this vector does not itself have a GATC nucleotide sequence. In addition, the BamHI fragments 1.9 and 1.8 kb in size present in the 5.7 kb KpnI fragment are subcloned into the BamHI cleavage site of pBRKanf4, resulting the plasmids pTS006 and pTS007, and pTS008 and pTS009, respectively.

To prepare subclones sequentially truncated by Sau3A fragments for the DNA sequencing, the plasmids pTS004 to pTS009 are partially digested with Sau3A and completely digested with XbaI or HindIII (a cleavage site in the multiple cloning region of the vector). The DNA obtained in this way (consisting of the linearized vector with inserted DNA fragments truncated by Sau3A fragments) is filled in at the ends using Klenow polymerase (fragment of polymerase I, see Maniatis *et al.* pages 113-114), self-ligated with T4 DNA ligase and transformed into *E. coli* DH5 α . The plasmid DNA which corresponds to the pTS004 to pTS009 plasmids, but has DNA regions, which are truncated from one side by Sau3A fragments, from the original integrated fragments of *A. mediterranei*, is isolated from individual transformed clones obtained in this way.

The DNA sequencing is carried out with the plasmids obtained in this way and with pTS004 to pTS009 using the reaction kit from Perkin-Elmer/Applied Biosystems with dye-labelled terminator reagents (Kit N° 402122) and a universal primer or a T7 primer. A standard cycle sequencing protocol with a thermocycler (MJ Research DNA Engine Thermocycler, Model 225) is used, and the sequencing reactions are analysed by the Applied Biosystems automatic DNA sequencer (Modell 373 or 377) in accordance with the manufacturer's instructions. To analyse the results, the following computer programs (software) are employed: Applied Biosystems DNA analysis software, Unix Solaris CDE software, DNA assembly and analysis package GAP licensed from R. Staden (Nucleic Acid Research (1995)23, 1406-1410) and Blast (NCBI).

The methods described above can be used to sequence completely both DNA strands of the 5.7 kb KpnI fragment from *A. mediterranei* strain wt3136. The DNA sequence of the 5.7 kb fragment with a length of 5676 base pairs is depicted in SEQ ID NO 1.

Example 6: Analysis of the protein-encoding region (genes) on the 5.7 kb KpnI fragment from *A. mediterranei*

The nucleotide sequence of the 5.7 kb KpnI fragment is analysed using the Codonpreference computer program (Genetics Computer Group, University of Wisconsin, 1994). This analysis shows that this fragment is over its whole length a protein-encoding region and thus forms part of a larger open reading frame (ORF). The codons used in this ORF are typical of

streptomycetes and actinomycetes genes. The amino acid sequence derived from the DNA sequence from this ORF is depicted in SEQ ID NO 2.

Polyketide synthases for macrolide antibiotics (such as erythromycin, rapamycin) are very large multifunctional proteins which comprise several enzymatically active domains which are now well characterized (Hopwood und Khosla, Ciba Foundation Symposium (1992), 171, 88-112; Donadio and Katz, Gene (1992), 111, 51-60; Schwecke et al., Proc. Natl. Acad. Sci. U.S.A. (1995) 92 (17), 7839-7843). Comparison of the amino acid sequence depicted in SEQ ID NO 2 with that of the very well-characterized erythromycin polyketide synthase, *eryA* ORF1 (Donadio, Science, (1991) 252, 675-679, DNA sequence gene/EMBL accession NO M63676) gives the following results:

Region from SEQ ID NO 2: amino acids 2 - 325: is 40% identical to the acyltransferase domain of module 2 of the *eryA* locus of *Saccharopolyspora erythraea*.

Region from SEQ ID NO 2: amino acids 325 - 470: is 43% identical to the dehydratase domain of module 4 of the *eryA* locus of *Saccharopolyspora erythraea*.

Region from SEQ ID NO 2: amino acids 762 - 940: is 48% identical to the ketoreductase domain of module 2 of the *eryA* locus of *Saccharopolyspora erythraea*.

Region from SEQ ID NO 2: amino acids 1024- 1109: is 57% identical to the acyl carrier protein domain of module 2 of the *eryA* locus of *Saccharopolyspora erythraea*.

Region from SEQ ID NO 2: amino acids 1126 - 1584: is 59% identical to the ketoacyl synthase domain of module 1 of the *eryA* locus of *Saccharopolyspora erythraea*.

The very large similarities found in the amino acid sequence and in the size and arrangement of the enzymatic domains suggest that the cloned KpnI region 5.7 kb in size from *A. mediterranei* codes for part of a polyketide synthase which is typical of polyketides of the macrolide type.

Example 7: Construction of a cosmid gene bank from *A. mediterranei*

The cosmid vector employed is the plasmid pWE15 which can be purchased (Stratagene, La Jolla, CA, USA). pWE15 is completely cut with the enzyme BamHI (Maniatis *et al.* 1989) and precipitated with ethanol. For ligation to the cosmid DNA, chromosomal DNA from *A. mediterranei* is isolated as described in Example 1 and partially digested with the restriction enzyme Sau3A (Böhringer, Mannheim) to form DNA fragments most of which have a size of 20 - 40 kb. The DNA pretreated in this way is fractionated by fragment size by centrifugation (83,000 g, 20°C) on a 10% to 40% sucrose density gradient for 18 h. The gradient is fractionated in 0.5 ml aliquots and dialysed, and samples of 10 µl are analysed on a 0.3% agarose gel with DNA size standard. Fractions with chromosomal DNA 25 - 40 kb in size are combined, precipitated with ethanol and resuspended in a small volume of water.

Ligation of the cosmid DNA to the *A. mediterranei* Sau3A fragments isolated according to their size (see above) takes place with the aid of a T4-DNA ligase. About 3 µg of each of the two DNA starting materials are employed in a reaction volume of 20 µl, and the ligation is carried out at 12°C for 15 h. 4 ml of this ligation mixture are packaged into lambda phages using the *in vitro* packaging kit which can be purchased from Stratagene (La Jolla, CA, USA) (in accordance with the manufacturer's instructions). The resulting phages are introduced by infection into the *E. coli* strain X-1BlueMR[®] (Stratagene). Titration of the phage material reveals about 20,000 phage particles per ml, analysis of 12 cosmid clones shows that all the clones contain plasmid DNA inserts 25 - 40 kb in size.

Example 8: Identification, cloning and characterization of the chromosomal *A. mediterranei* DNA region which is adjacent to the cloned 5.7 kb KpnI fragment

To identify and clone the chromosomal *A. mediterranei* DNA region which is adjacent to the 5.7 kb KpnI fragment described above in Examples 3 and 5, firstly a radioactive DNA probe is prepared from this 5.7 kb KpnI fragment. This is done by radiolabelling approximately 0.5 µg of the isolated DNA fragment with ³²P-d-CTP by the nick translation system of Gibco/BRL (Basle) in accordance with the manufacturer's instructions.

Infection of *E. coli* X-1 Blue MR (Stratagene) with an aliquot of the lambda phages packaged *in vitro* (see Example 7) results in more than 2000 clones on several LB + ampicillin (50 µg/ml) plates. These clones are tested by colony hybridization on nitrocellulose filters (see Example 3 for method). The DNA probe used is the 5.7 kb KpnI DNA fragment from *A. mediterranei* which is radiolabelled with ³²P-d-CTP and was prepared above.

5 cosmid clones showing a significant signal with the DNA probe are found. The plasmid DNA of these cosmids is isolated (Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989), digested with KpnI and analysed in an agarose gel. Analysis reveals that all 5 plasmids have integrated chromosomal *A. mediterranei* DNA with a size of the order of about 25-35 kb, and all contain the 5.7 kb KpnI fragment.

To characterize the chromosomal *A. mediterranei* DNA region which is adjacent to the cloned KpnI fragment, the plasmid DNA of one of the 5 cosmid clones is subjected to restriction analysis. The selected plasmid of the cosmid clone has the number pNE112 and likewise comprises the 13 kb BglII fragment described in Example 3.

Digestion of the plasmid pNE112 with the restriction enzymes BamHI, BglII, HindIII (singularly and in combination) allows a restriction map of the cloned region of *A. mediterranei* to be prepared, and this permits this region about 26 kb in size in the chromosome of *A. mediterranei* to be characterized. This region is characterized by the following restriction cleavage sites with the stated distance in kb from one end: BamHI in position 3.2 kb, HindIII in position 6.6 kb, BglII in position 11.5 kb, BamHI in position 16.6 kb, BamHI in position 17.3 kb, BamHI in position 21 kb and BglII in position 24 kb.

Example 9: Determination of the sequence of the chromosomal *A. mediterranei* DNA region present in the plasmid pNE112 and overlapping with the cloned 5.7 kb KpnI fragment

The plasmid pNE112 DNA is split up into fragments directly using an Aero-Mist nebulizer (CIS-US Inc., Bedford, MA, USA) under a nitrogen pressure of 8-12 pounds per square inch. These random DNA fragments are treated with T4 DNA polymerase, T4 DNA kinase and *E. coli* DNA polymerase in the presence of the 4 dNTPs in order to generate blunt ends

on the double-stranded DNA fragments (Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989). The fragments are then fractionated in 0.8% low melting agarose (FMC SeaPlaque Agarose, Catalogue N° 50113), and fragments 1.5-2 kb in size are extracted by hot phenol extraction (Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989). The DNA fragments obtained in this way are then ligated with the aid of T4 DNA ligase to the plasmid vector pBRKanf4 (see Example 5) or pBlueScript KS+ (Stratagene, La Jolla, CA, USA), each of which is cut once with square ends by appropriate restriction digestion (SmaI for pBRKanf4 and EcoRV for pBlueScript KS+), and is dephosphorylated on the ends by a treatment with alkaline phosphatase (Böhringer, Mannheim). The ligation mixture is then transformed into *E. coli* DH5 α , and the cells are incubated overnight on LB agar with the appropriate antibiotic (kanamycin 40 μ g/ml for pBRKanf4, ampicillin 100 μ g/ml for pBlueScript KS+). Grown colonies are transferred singly into 1.25 ml of liquid TB medium with antibiotic in 96-well plates with wells of a volume of 2 ml, and incubated at 37°C overnight. Template DNA for the sequencing is prepared directly from these cultures by alkaline lysis (Birnboim, Methods in Enzymology (1983) 100, 243-255). The DNA sequencing takes place using the Perkin Elmer/Applied Biosystems reaction kit with dye-labelled terminator reagents (Kit N° 402122) and universal M13 mp18/19 primers or T3, T7 primers, or with primers prepared by us which bind to internal sequences. A standard cycle sequencing protocol with 20 cycles is used with a thermocycler (MJ Research DNA Engine Thermocycler, Model 225). The sequencing reactions are precipitated with ethanol, resuspended in formamide loading buffer and fractionated and analysed by electrophoresis using the Applied Biosystems automatic DNA sequencer (Model 377) in accordance with the manufacturer's instructions. Sequence files are produced with the aid of the Applied Biosystems DNA Analysis Software computer program and transferred to a SUN UltraSpark computer for further analysis. The following computer programs (software) are employed for analysing the results: DNA assembly and analysis package GAP (Genetics Computer Group, University of Wisconsin, R. Staden, Cambridge University UK) and the four programs: Phred, Cross-match, Phrad and Consed (P. Green, University of Washington, B. Ewing and D. Gordon, Washington University in Saint Louis). After the original sequences have been connected together to give longer coherent sequences (contigs), missing DNA sections are specifically sequenced with the aid of new primers (binding to sequenced sections), or by longer sequencing or sequencing the other strand.

It is possible with the method described above to sequence the entire chromosomal DNA region 26 kb in size from *A. mediterranei* which is cloned in pNE112. The DNA sequence is depicted in SEQ ID NO 3 in the base pair 27801 - 53789 section. The DNA sequence of the 5.7 kb KpnI fragment described in Example 5 is present in pNE112, and is depicted in SEQ ID NO 3 in the base pair 43093 - 48768 region.

Example 10: Identification and characterization of cosmid clones with chromosomal DNA fragments from *A. mediterranei* which overlap with one end of the 26 kb *A. mediterranei* region of pNE112

To identify cosmid clones which comprise chromosomal DNA fragments from *A. mediterranei* located directly in front of the 26 kb region of pNE112, the plasmid pNE112 is cut with the restriction enzyme BamHI, and the resulting BamHI fragment 3.2 kb in size is separated from the other BamHI fragments in an agarose gel and isolated from the gel. This BamHI fragment is located at one end of the incorporated *A. mediterranei* DNA in pNE112 (see Example 8) and can thus be used as DNA probe for finding the required cosmid clones. Approximately 0.5 µg of the isolated 3.2 kb BamHI DNA fragment is radiolabelled with ³²P-dCTP by the nick translation system from Gibco/BRL (Basel) in accordance with the manufacturer's instructions.

The cosmid gene bank from *A. mediterranei* described in Example 7 is then analysed by colony hybridization (Method of Example 3) using this 3.2 kb DNA probe for clones with overlaps. Two cosmid clones with a strong hybridization signal can be identified in this way and are given the numbers pNE95 and pRi44-2. It is possible by restriction analysis and Southern blot to confirm that the plasmids pNE95 and pRi44-2 comprise chromosomal DNA fragments from *A. mediterranei* which overlap with the 3.2 kb BamHI fragment from pNE112 and together cover a 35 kb chromosomal region of *A. mediterranei* which is directly adjacent to the 26 kb *A. mediterranei* fragment of pNE112 cloned in pNE112.

Example 11: Restriction analysis of the chromosomal *A. mediterranei* DNA region cloned with the cosmid clones pNE112, pNE95 and pRi44-2

The chromosomal *A. mediterranei* DNA region cloned with the cosmid clones pNE112, pNE95 and pRi44-2 is characterized by carrying out a restriction analysis. Digestion of the plasmid DNA of the three cosmids with the restriction enzymes EcoRI, BglII and HindIII (singly and in combination) produces a rough restriction map of the cloned region of *A. mediterranei*. Overlapping fragments of the three plasmids are in this case established and confirmed by Southern blot. This chromosomal region of *A. mediterranei* has a size of about 61 kb and is characterized by the following restriction cleavage sites with the stated distance in kb from one end: EcoRI in position 7.2 kb, HindIII in position 21 kb, BglII in position 31 kb, HindIII in position 42 kb, BglII in position 47 kb and BglII in position 59 kb. In this region in the *A. mediterranei* chromosome, the plasmid pRi 44-2 covers a region from position 1 to approximately 37 kb, plasmid pNE95 covers a region of approximate position 9 kb - 51 kb and plasmid pNE 112 covers a region of approximate position 35 kb - 61 kb.

Example 12: Determination of the sequence of the chromosomal *A. mediterranei* DNA region described in Example 11 from the EcoRI cleavage site in the 7.2 kb position up to the 61 kb end

Determination of the DNA sequence of the chromosomal region described in Example 11 from *A. mediterranei* (EcoRI cleavage site in the 7.2 kb position to 51 kb) is carried out with the plasmids pRi 44-2 and pNE95, using exactly the same method as described in Example 9. Analysis of the DNA sequence obtained in this way confirms the rough restriction map described in Example 11 and the overlaps of the cloned *A. mediterranei* fragments in the plasmids pNE112, pNE95 and pRi44-2.

The DNA sequence of the chromosomal *A. mediterranei* DNA region described in Example 11 from the EcoRI cleavage site in the 7.2 kb position up to the end at 61 kb is depicted in SEQ ID NO 3 (length 53789 base pairs).

Example 13: Analysis of a first protein-encoding region (ORF A) of the cloned *A. mediterranei* chromosomal region depicted in SEQ ID NO 3

The nucleotide sequence shown in SEQ ID NO 3 is analysed with the Codonpreference computer program (Genetics Computer Group, University of Wisconsin, 1994). This analysis shows that a very large open reading frame (ORF A) which codes for a protein is present in

the first third of the sequence (position 1825 - 15543 including stop codon in SEQ ID NO 3). The codons used in ORF A are typical of actinomycetes genes with a high G+C content.

Comparison of the amino acid sequence of ORF A (SEQ ID NO 4, size 4572 amino acids) with other polyketide synthases and specifically with the very well characterized polyketide synthase of *Saccharopolyspora erythraea* (Donadio, Science, (1991) 252, 675-679, DNA sequence gene/EMBL accession N° M63676) gives the following results:

Region from ORF A, SEQ ID NO 4: amino acids 370 - 451: is 50% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region from ORF A, SEQ ID NO 4: amino acids 469 - 889: is 65% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region from ORF A, SEQ ID NO 4: amino acids 982 - 1292: is 54% identical to the acyl-transferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region from ORF A, SEQ ID NO 4: amino acids 1324 - 1442: is 42% identical to the dehydratase domain of module 4 of the eryA locus of *Saccharopolyspora erythraea*.

Region from ORF A, SEQ ID NO 4: amino acids 1664 - 1840: is 56% identical to the keto-reductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region from ORF A, SEQ ID NO 4: amino acids 1929 - 2000: is 53% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region from ORF A, SEQ ID NO 4: amino acids 2032 - 2453: is 64% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region from ORF A, SEQ ID NO 4: amino acids 2554 - 2865: is 37% identical to the acyl-transferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region from ORF A, SEQ ID NO 4: amino acids 2918 - 2991: is 54% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region from ORF A, SEQ ID NO 4: amino acids 3009 - 3431: is 65% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region from ORF A, SEQ ID NO 4: amino acids 3532 - 3847: is 53% identical to the acyl-transferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF A, SEQ ID NO 4: amino acids 4142 - 4307: is 43% identical to the keto-reductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF A, SEQ ID NO 4: amino acids 4405 - 4490: is 50% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

In addition to these significant homologies with the eryA polyketide synthase of *S. erythraea*, the region of ORF A, SEQ ID NO 4: amino acids 1 - 356 is 53% identical to the postulated starter unit activation domain of the rapamycin polyketide synthase from *Streptomyces hygroscopicus* (Aparicio et al. GENE (1996) 169, 9-16)

The great similarities found in the amino acid sequence of the enzymatic domains suggest unambiguously that the protein-encoding region (ORF A) of the *A. mediterranei* chromosomal region depicted in SEQ ID NO 3 codes for a typical modular (type 1) polyketide synthase. This very large *A. mediterranei* polyketide synthase encoded by ORF A comprises three complete bioactive modules which are each responsible for condensation of a C2 unit in the macrolide ring of the molecule and correct modification of the initially formed β -keto groups. Because of the homology with activating domains of the rapamycin polyketide synthase, the first module described above very probably comprises an enzymatic domain for activating the aromatic starter unit of rifamycin biosynthesis, 3-amino-5-hydroxybenzoic acid (Ghisalba et al., Biotechnology of Industrial Antibiotics Vandamme E. J. Ed., Decker Inc. New York, (1984) 281-327).

Example 14: Analysis of a second protein encoding region (ORF B) of the cloned *A. mediterranei* chromosomal region depicted in SEQ ID NO 3

The nucleotide sequence in SEQ ID NO 3 is analysed using the Codonpreference computer program (Genetics Computer Group, University of Wisconsin, 1994). This analysis shows that another large open reading frame (ORF B) which codes for a protein is present in the middle region of the sequence (position 15550 - 30759 including stop codon in SEQ ID NO 3). The codons used in ORF B are typical of actinomycetes genes with a high G+C content.

Comparison of the amino acid sequence of ORF B (SEQ ID NO 5, length 5069 amino acids) with other polyketide synthases and specifically with the very well characterized polyketide synthase of *Saccharopolyspora erythraea* (Donadio, Science, (1991) 252, 675-679, DNA sequence gene/EMBL accession N° M63676) gives the following results:

Region of ORF B, SEQ ID NO 5: amino acids 44 - 468: is 62% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 571 - 889: is 56% identical to the acyl-transferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 921 - 1055: is 47% identical to the dehydratase domain of module 4 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 1353 - 1525: is 49% identical to the keto-reductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 1621 - 1706: is 53% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 1726 - 2148: is 62% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 2251 - 2560: is 55% identical to the acyl-transferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 2961 - 3132: is 49% identical to the keto-reductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 3228 - 3313: is 52% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 3332 - 3755: is 63% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 3857 - 4173: is 52% identical to the acyl-transferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 4664 - 4799: is 47% identical to the keto-reductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 4929 - 5014: is 52% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Example 15: Analysis of a third protein-encoding region (ORF C) of the cloned *A. mediterranei* chromosomal region depicted in SEQ ID NO 3

The nucleotide sequence in SEQ ID NO 3 is analysed using the Codonpreference computer program (Genetics Computer Group, University of Wisconsin, 1994). This analysis shows that a large open reading frame (ORF C) which codes for a protein is present in the middle region of the sequence (position 30895 - 36060 including stop codon in SEQ ID NO 3). The codons used in ORF C are typical of actinomycetes genes with a high G+C content.

Comparison of the amino acid sequence of ORF C (SEQ ID NO 6, length 1721 amino acids) with other polyketide synthases and specifically with the very well characterized polyketide synthase from *Saccharopolyspora erythraea* (Donadio, Science, (1991) 252, 675-679, DNA sequence gene/EMBL accession N° M63676) gives the following results:

Region of ORF C, SEQ ID NO 6: amino acids 1 - 414: is 63% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF C, SEQ ID NO 6: amino acids 514 - 828: is 54% identical to the acyl-transferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF C, SEQ ID NO 6: amino acids 1290 - 1399: is 49% identical to the keto-reductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF C, SEQ ID NO 6: amino acids 1563 - 1648: is 55% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Example 16: Analysis of a fourth protein-encoding region (ORF D) of the cloned *A. mediterranei* chromosomal region depicted in SEQ ID NO 3

The nucleotide sequence in SEQ ID NO 3 is analysed using the Codonpreference computer program (Genetics Computer Group, University of Wisconsin, 1994). This analysis shows that a large open reading frame (ORF D) which codes for a protein is present in the middle region of the sequence (position 36259 - 41325 including stop codon in SEQ ID NO 3). The codons used in ORF D are typical of actinomycetes genes with a high G+C content.

Comparison of the amino acid sequence of ORF D (SEQ ID NO 7, length 1688 amino acids) with other polyketide synthases and specifically with the very well characterized polyketide synthase from *Saccharopolyspora erythraea* (Donadio, Science, (1991) 252, 675-679, DNA sequence genes/EMBL accession N° M63676) gives the following results:

Region of ORF D, SEQ ID NO 7: amino acids 1 - 418: is 64% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF D, SEQ ID NO 7: amino acids 524 - 841: is 54% identical to the acyl-transferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF D, SEQ ID NO 7: amino acids 1260 - 1432: is 51% identical to the keto-reductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF D, SEQ ID NO 7: amino acids 1523 - 1608: is 53% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Example 17: Analysis of a fifth protein-encoding region (ORF E) of the cloned *A. mediterranei* chromosomal region depicted in SEQ ID NO 3

The nucleotide sequence in SEQ ID NO 3 is analysed using the Codonpreference computer program (Genetics Computer Group, University of Wisconsin, 1994). This analysis shows that a large open reading frame (ORF E) which codes for a protein is present in the rear region of the sequence (position 41373 - 51614 including stop codon in SEQ ID NO 3). The codons used in ORF E are typical of actinomycetes genes with a high G+C content.

Comparison of the amino acid sequence of ORF E (SEQ ID NO 8, length 3413 amino acids) with other polyketide synthases and specifically with the very well characterized polyketide synthase from *Saccharopolyspora erythraea* (Donadio, Science, (1991) 252, 675-679, DNA sequence gene/EMBL accession N° M63676) gives the following results:

Region of ORF E, SEQ ID NO 8: amino acids 31 - 451: is 64% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF E, SEQ ID NO 8: amino acids 555 - 874: is 37% identical to the acyl-transferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF E, SEQ ID NO 8: amino acids 907 - 1036: is 49% identical to the dehydratase domain of module 4 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF E, SEQ ID NO 8: amino acids 1336 - 1500: is 52% identical to the keto-reductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF E, SEQ ID NO 8: amino acids 1598 - 1683: is 51% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF E, SEQ ID NO 8: amino acids 1702 - 2124: is 62% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF E, SEQ ID NO 8: amino acids 2229 - 2543: is 53% identical to the acyl-transferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF E, SEQ ID NO 8: amino acids 2573 - 2700: is 47% identical to the dehydratase domain of module 4 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF E, SEQ ID NO 8: amino acids 3054 - 3227: is 52% identical to the keto-reductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF E, SEQ ID NO 8: amino acids 3324 - 3405: is 51% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Example 18: Analysis of a sixth protein-encoding region (ORF F) of the cloned *A. mediterranei* chromosomal region depicted in SEQ ID NO 3

The nucleotide sequence in SEQ ID NO 3 is analysed using the Codonpreference computer program (Genetics Computer Group, University of Wisconsin, 1994). This analysis shows that an open reading frame (ORF F) which codes for a protein is present in the rear region of the sequence (position 51713 - 52393 including stop codon in SEQ ID NO 3). The codons used in ORF F are typical of actinomycetes genes with a high G+C content.

Comparison of the amino acid sequence of ORF F (SEQ ID NO 9, length 226 amino acids) with proteins from the EMBL databank (Heidelberg) shows a great similarity with the N-hydroxyarylamine O-acyltransferase from *Salmonella typhimurium* (29% identity over a region of 134 amino acids). There is also significant homology with arylamine acyl-transferases from other organisms. It can be concluded from these agreements that the ORF F found in *A. mediterranei* in SEQ ID No 3 codes for an arylamine acyl transferase, and it can be assumed that this enzyme is responsible for the linkage of the long acyl chain produced by the polyketide synthase to the amino group on the starter molecule, 3-amino-5-hydroxybenzoic acid. This reaction would close the rifamycin ring system correctly after completion of the condensation steps by the polyketide synthase.

Example 19: Summarizing assessment of the function of the proteins encoded by ORF A - F in SEQ ID NO 3, and their role in the biosynthesis of rifamycin

The five protein-encoding regions (ORF A-E), described in Examples 13 - 17, of SEQ ID NO 3 comprise proteins with very great similarity (in the amino acid sequence and the arrangement of the enzymatic domains) to polyketide synthases for polyketides of the macrolide type. Taken together, these five multifunctional enzymes comprise 10 polyketide

synthase modules which are each responsible for a condensation step in the polyketide synthesis. 10 such condensation steps are likewise necessary for rifamycin biosynthesis (Ghisalba et al., *Biotechnology of Industrial Antibiotics* Vandamme E. J. Ed., Decker Inc. New York, (1984) 281-327). The processing of the particular keto groups required by the enzymatic domains within the modules substantially corresponds to the activity required by the rifamycin molecule, if it is assumed that the polyketide synthesis takes place "colinearly" with the arrangement of the modules in the gene cluster of *A. mediterranei* (this is so for other macrolide antibiotics such as erythromycin and rapamycin). It may be added here that it is not certain whether transcription of the five ORFs results in five proteins; in particular, ORF C and ORF D might possibly be translated to a large protein.

An enzymatic domain which is very probably responsible for activating the starter molecule, 3-hydroxy-5-aminobenzoic acid, of rifamycin biosynthesis can be found at the N terminus of ORF A, the start of the polyketide synthase. Directly below the described rifamycin polyketide synthase gene cluster there is a gene (ORF F) which very probably determines a protein which brings about ring closure of the rifamycin molecule after completion of the condensation steps by the polyketide synthase.

It can be concluded on the basis of these findings that the *A. mediterranei* chromosomal region described in SEQ ID NO 3 is responsible for the ten condensation steps required for rifamycin polyketide synthesis, including activation of the starter molecule 3-hydroxy-5-aminobenzoic acid, and the concluding ring closure.

Deposited microorganisms

The following microorganisms and plasmids have been deposited at the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM), Mascheroder Weg 1b, D-38124 Braunschweig, in accordance with the requirements of the Budapest Treaty.

Microorganism/Plasmid	Date of deposit	Deposit number
<i>E. coli</i> with plasmid pRi7-3	10.08.96	DSM 11114
<i>E. coli</i> with plasmid pNE112	14.07.97	DSM 11657
<i>E. coli</i> with plasmid pNE95	14.07.97	DSM 11656
<i>E. coli</i> with plasmid pRi44-2	14.07.97	DSM 11655

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

- (A) NAME: Novartis AG
- (B) STREET: Schwarzwaldallee 215
- (C) CITY: Basel
- (E) COUNTRY: Switzerland
- (F) POSTAL CODE (ZIP): 4058
- (G) TELEPHONE: +41 61 324 1111
- (H) TELEFAX: + 41 61 322 75 32

(ii) TITLE OF INVENTION: Rifamycin biosynthesis gene cluster

(iii) NUMBER OF SEQUENCES: 9

(iv) COMPUTER READABLE FORM:

- (A) MEDIUM TYPE: Floppy disk
- (B) COMPUTER: IBM PC compatible
- (C) OPERATING SYSTEM: PC-DOS/MS-DOS
- (D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

GGTACCCGGT GTTCGCGACG GCGTTCGACG AGGCTTGCGA GCAGCTGGAC GTCTGTCTGG	60
CCGGCCGTGC CGGGCACCGC GTGCGGGACG TCGTGCTCGG CGAAGTGCCC GCCGAAACCG	120
GGCTGCTGAA CCAGACGGTC TTCACCCAAG CCGGGCTGTT CGCGGTGGAG AGCGCGCTGT	180
TCCGGCTCGC CGAATCCTGG GGTGTCCGCG CCGACGTGGT GCTCGGCCAC TCCATCGGGG	240
AGATCACCGC CGCGTATGCC GCGGGCGTCT TCTCGCTGCC GGACGCCGCC CGGATCGTCG	300
CGGCGCGCGG CCGGCTGATG CAGGCGCTGG CGCCGGGCGG GCGGATGGTC GCCGTCGCCG	360
CCTCCGAAGC CGAGGTGGCC GAACTGCTCG GCGACGGCGT GGAACTCGCC GCCGTCAACG	420
GCCCTTCGGC GGTAGTCCTT TCCGGGGACG CCGACGCGGT CGTCGCGGCC GCCGCCCCGA	480
TGCGCGAGCG CGGGCACAAG ACCAAGCAGC TCAAGGTTTC GCACGCGTTC CACTCCGCGC	540
GGATGGCGCC GATGCTGGCG GAGTTCGCCG CCGAGCTGGC CGGCGTGACG TGGCGCGAGC	600
CGGAGATCCC GGTGGTCTCC AACGTGACCG ECCGGTTCGC CGAGCCCGGC GAACTGACCG	660
AGCCGGGCTA CTGGGCCGAG CACGTGCGGC GGCCGGTGCG GTTCGCCGAG GCGGTCGCGG	720
CCGCGACGGA GTCCGGCGGC TCGCTGTTCG TGGAGCTCGG GCCGGGGGCG GCGCTGACCG	780
CCCTCGTCGA GGAGACGGCC GAGGTACACT GCGTCGCGGC CCTGCGGGAC GACCGCCCGG	840
AGGTCACCGC GCTGATCACC GCGGTGCGCG AGCTGTTCGT CCGCGGGGTT GCGGTGATT	900
GGCCGGCCCT GCTGCCGCCG GTCACCGGGT TCGTCGACCT GCCGAAGTAC GCCTTCGACC	960
AGCAGCACTA TTGGCTGCAG CCCGCCGCGC AGGCCACGGA CGCGGCCTCG CTCGGGCAGG	1020

TCGCGGCCGA	CCACCCGCTG	CTGGGCGCGG	TGGTCCGGCT	GCCGCAGTCG	GACGGCCTGG	1080
TCTTCACCTC	GCGGCTGTCA	TTGAAATCGC	ACCCGTGGCT	GGCCGACCAC	GTCATCGGCG	1140
GGGTGGTGCT	CGTCGCGGGC	ACCGGGCTCG	TCGAGCTGGC	CGTCCGGGCC	GGGGACGAGG	1200
CCGGCTGCCC	GGTCTCGAA	GAATCGTCA	TCGAGGCTCC	GCTGGTCGTC	CCCGACCACG	1260
GCGGGGTCCG	GATCCAGGTC	GTCGTGGGGG	CACCGGGGGA	GACCGGTTTCG	CGCGCGGTTCG	1320
AGGTGTACTC	CCTGCGCGAG	GACGCCGGTG	CCGAAGTGTG	GGCCCGGCAC	GCCACCGGGT	1380
TCCTGGCTGC	GACGCCGTGC	CAGCACAAGC	CGTTCGACTT	CACCGCCTGG	CCGCCGCCCG	1440
GCGTCGAGCG	CGTCGACGTC	GAGGACTTCT	ACGACGGCTT	CGTCGACCGC	GGGTACGCCT	1500
ACGGGCCGTC	GTTCCGGGGC	CTGCGGGCGG	TGTGGCGGGC	CGGCGACGAA	GTGTTGCGCG	1560
AGGTGCCCCCT	GGCCGAGGAC	GACCGCGCGG	ACGCGGCCCG	GTTCCGGCATC	CACCCCGGCC	1620
TGCTGGACGC	CGCCCTGCAC	GCGGGCATGG	CCGGTGCCAC	CACCACGGAA	GAGCCCGGCC	1680
GGCCGGTGCT	GCCGTTCCGC	TGGAACGGCC	TGGTGCTGCA	CGCGGCCGGG	GCGTCCGCGC	1740
TGCGGGTCCG	GCTCGCCCCG	AGCGGTCCGG	ACGCCCTGTC	GGTCGAGGCC	GCGGACGAGG	1800
CCGGCGGTCT	CGTTGTGACG	GCGGACTCGC	TGGTCTCCCG	GCCGGTGTCG	GCCGAACAGC	1860
TGGGCGCGGC	GGCGAACCAC	GACGCGTTGT	TCCGCGTGGA	GTGGACCGAG	ATTTCTCTCGG	1920
CTGGAGACGT	TCCGGCGGAC	CACGTCGAAG	TGCTCGAAGC	CGTCGGCGAG	GATCCCCCTGG	1980
AACTGACCGG	CCGGGTCCCTG	GAGGCCGTGC	AGACCTGGCT	CGCCGACGCA	GCCGACGACG	2040
CTCGCCTGGT	CGTGGTGACC	CGCGGCGCCG	TCCACGAGGT	GACTGACCCG	GCCGGTGCCG	2100
CGGTGTGGGG	CCTGATCCGG	GCCGCGCAGG	CGGAAAACCC	GGACCGGATC	GTGCTGCTGG	2160

ACACCGACGG TGAAGTGCCG CTAGGCCGGG TGCTGGCCAC CGGCGAGCCC CAAACAGCCG	2220
TCCGAGGCGC CACGCTGTTC GCCCCGCGGC TGGCCCGCGC CGAGGCCGCG GAGGCACCGG	2280
CAGTGACCGG CGGGACGGTC CTGATCTCGG GCGCCGGCTC GCTGGGCGCG CTCACCGCCC	2340
GGCACCTGGT CCCCCGGCAC GGAGTCCGGC GGCTGGTGCT CGTCAGCCGC CGTGGCCCCG	2400
ACGCCGACGG CATGGCCGAA CTGACCGCTG AACTCATCGC TCAGGGCGCC GAGGTGCGCC	2460
TAGTCGCTTG CGACCTGGCC GACCGGGACC AGGTCCGGGT ACTGCTGGCC GAGCACCGCC	2520
CGAACCCCGT CGTGACACG GCCGGTGTTT TCGACGACGG CGTCTTCGAG TCGCTGACGC	2580
GGGAGCGGCT GGCCAAGGTC TTCGCGCCCA AAGTTACTGC TGCCAATCAC CTCGACGAGC	2640
TGACCCGCGA ACTGGATCTT CGCGCGTTTC TCGTGTCTC CTCCGCCTCC GGGGTCTTCG	2700
GCTCCGCCGG GCAGGGCAAC TACGCCGCTG CCAACGCTA CCTGGACGCC GTGGTCGCCA	2760
ACCGCCGGGC CGCGGGCCTG CCCGGCACAT CGCTGGCCTG GGGCCTGTGG GAACAGACCG	2820
ACGGGATGAC CGCGACCTC GGCAGCGCCG ACCAGGCGCG GCGAGTCGC GCGGGGTCC	2880
TCGCCATCTC ACCCGCCGAA GGCATGGAGC TGTTCGACGC AGCGCCGGAC GGGCTCGTCG	2940
TCCCGGTCAA GCTGGACCTG CGCAAGACCC GCGCCGGCGG GACGGTGCCG CACCTGCTGC	3000
GCGGCCTGGT CCGCCCGGA CGGCAGCAGG CCCGTCCGGC GTCCACTGTG GACAACGGAC	3060
TGGCCGGGCG ACTCGCCGGG CTCGCGCCGG CGGAGCAGGA GGCGCTGCTG CTCGACGTCG	3120
TCCGCACGCA GGTGCGCTG GTGCTCGGGC ACGCCGGGCC GGAGGCCGTC CGCGCGGACA	3180
CGGCGTTCAA GGACACCGGC TTCGACTCGC TGACGTGGT GGAAC'TGCGC AACC'GGCTGC	3240

GCGAGGCGAG CGGGCTGAAG CTGCCCCGGA CGCTCGTCTT CGACTACCCG ACGCCGGTCG 3300

CGCTGGCCCG CTACCTGCGT GACGAATTCG GCGACACGGT GGCAACAACCT CCGGTGGCCA 3360

CCGCGGCCGC AGCGGACGCC GCGAGCCGA TCGCCATCGT CGGCATGGCG TGCCGGCTGC 3420

CGGGCGGGGT CACCGATCCC GAAGGCCTGT GCGCCTGGT GCGCGACGGC CTCGAAGGGC 3480

TGTCTCCCTT CCCCAGAGAC CGGGGCTGGG ACCTGGAGAA CCTGTTCGAC GACGACCCCG 3540

ACCGCTCCGG CACGACGTAC ACCAGCCGGG GCGGGTTCCT CGACGGCGCC GGCCTGTTCG 3600

ACGCGGGCTT CTTCCGGATT TCGCCGCGG AGGCGCTGGC CATGGACCCG CAGCAGCGGC 3660

TGCTGCTCGA GGCGGCTGG GAAGCCCTCG AAGGCACCGG TGTCGACCCG GGCTCGTTGA 3720

AGGGCGCCGA CGTCGGGGTG TTCGCCGGG TGTCCAACCA GGGCTATGGG ATGGGCGCGG 3780

ATCCGGCCGA ACTGGCGGGG TACGCGAGCA CGCGGGCGC TTCGAGCGTC GTCTCGGGCC 3840

GAGTCTCGTA CGTCTTCGGG TTCGAAGGAC CGCGGGTCAC GATCGACACG GCTTCTCGT 3900

CGTCGCTGGT GGCGATGCAC CTGGCCGGG AGGCGCTGCG GCAGGGCGAG TGCTCGATGG 3960

CCCTGGCCCG TGGCGTCACG GTGATGGGGA CGCCGGCAC GTTCGTGGAG TTCGCGAAGC 4020

AGCGCGGCTT GGCCGGCGAC GGCCGGTGCA AGCCCTACGC CGAAGGCGCG GACGGCACGG 4080

GCTGGGCCGA GGGCGTCGGG GTCGTCGTGC TGGAGCGGCT GTCGGTGGCG CGCGAGCGCG 4140

GGCACCGGGT GCTGGCCGTG CTGCGCGGCA GCGCGGTCAA CTCGACGGC GCGTCCAACG 4200

GCCTGACCGC CCCCAACGGG CCGTCGCAGC AACGGGTGAT CCGCCGGGCC CTGGCCGGCG 4260

CCGGCCTCGA ACCGTCCGAT GTGGACATCG TGGAAGGGCA CGGCACCGG ACGGCGCTGG 4320

GCGACCCGAT CGAGGCGCAG GCCCTGCTGG CCACCTACGG CAAGGACCGC GACCCGGAGA 4380

CGCCGTTGTG GCTGGGGTCG GTGAAGTCGA ACTTCGGCCA CACGCAGTCC GCGGCCGGCG 4440

TGGCCGGGGT GATCAAGATG GTGCAGGCGC TGCGCCACGG CGTCATGCCG CCCACCCTGC 4500

ACGTGGACCG GCCCACCAGC CAGGTCGACT GGTCCGCGGG GGCCGTCGAA GTGCTGACCG 4560

AGGCACGGGA GTGGCCGCGG AACGGCCGTC CGCGCCGGGC CGGGGTGTCC TCGTTCGGGA 4620

TCAGCGGCAC GAACGCCCAC CTGATCATCG AAGAAGCACC GGCCGAGCCA CAGCTTGCCG 4680

GACCACCGCC GGACGGCGGT GTGGTGCCGC TGGTCGTCTC GGCTCGCAGC CCCGGTGCCC 4740

TGGCCGGTCA GGCGCGTCGG CTGGCCACGT TCCTCGGCGA CGGGCCCCCT TCCGACGTCC 4800

CCGGTGCCT GACGAGCCGC GCCCTGTTCG GCGAGCGCGC GGTCGTCTGT GCGGATTCCG 4860

CCGAGGAAGC CCGCGCCGGT CTGGGCGCAC TGGCCCGCGG CGAAGACGCG CCGGGCCTGG 4920

TCCGCGGCCG GGTGCCCCG TCCGGCCTGC CGGGCAAGCT CGTGTGGGTG TTCCCCGGGC 4980

AGGGGACGCA GTGGGTGGGC ATGGGCCGCG AACTCCTCGA AGAGTCTCCG GTGTTGCGCG 5040

AGCGGATCGC CGAGTGTGCG GCCGCGCTGG AGCCGTGGAT CGGCTGGTCG CTGTTGACG 5100

TCCTCCGTGG CGACGGTGAC CTCGATCGGG TCGATGTGCT GCAGCCCGCG TGCTTTGCGG 5160

TGATGGTCGG CTTGGCCGCG GTGTGGTCCT CGGCCGGGGT GGTCCCCGAT GCGGTGCTCG 5220

GCCACTCCCA GGGTGAGATC GCCGCGGCGT GCGTGTCCGG TGCCTTCTCG CTGGAGGATG 5280

CGGCGAAGGT GGTGCCCCTG CGCAGCCAGG CCATCGCCGC GAAGCTCTCC GGCCGCGGCG 5340

GGATGGCTTC GGTGCGCTTG GCGAAGCCG ATGTGGTGTG GCGGCTGGCG GACGGGGTCG 5400

AGGTGGCTGC CGTCAACGGT CCGGCGTCCG TGGTGATCGC GGGGGATGCC CAGGCCCTCG 5460

- 43 -

ACGAAACGCT GGAAGCGCTG TCCGGTCCGG GAATCCGGGC TCGGCGGGTG GCGGTGGACT 5520

ACGCCTCGCA CACCCGGCAC GTCGAAGACA TCGAAGACAC CCTCGCCGAA GCGCTGGCCG 5580

GGATCGACGC CCGGGCGCCG CTGGTGCCGT TCCTCTCCAC CCTCACCAGC GAGTGGATCC 5640

GGGACGAGGG CGTCGTGGAC GCGGGCTACT GGTACC 5676

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1891 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Tyr Pro Val Phe Ala Thr Ala Phe Asp Glu Ala Cys Glu Gln Leu Asp
1 5 10 15

Val Cys Leu Ala Gly Arg Ala Gly His Arg Val Arg Asp Val Val Leu
20 25 30

Gly Glu Val Pro Ala Glu Thr Gly Leu Leu Asn Gln Thr Val Phe Thr
35 40 45

Gln Ala Gly Leu Phe Ala Val Glu Ser Ala Leu Phe Arg Leu Ala Glu
50 55 60

Ser Trp Gly Val Arg Pro Asp Val Val Leu Gly His Ser Ile Gly Glu
65 70 75 80

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Ile Thr Ala Ala Tyr Ala Ala Gly Val Phe Ser Leu Pro Asp Ala Ala
85 90 95

Arg Ile Val Ala Ala Arg Gly Arg Leu Met Gln Ala Leu Ala Pro Gly
100 105 110

Gly Ala Met Val Ala Val Ala Ala Ser Glu Ala Glu Val Ala Glu Leu
115 120 125

Leu Gly Asp Gly Val Glu Leu Ala Ala Val Asn Gly Pro Ser Ala Val
130 135 140

Val Leu Ser Gly Asp Ala Asp Ala Val Val Ala Ala Ala Ala Arg Met
145 150 155 160

Arg Glu Arg Gly His Lys Thr Lys Gln Leu Lys Val Ser His Ala Phe
165 170 175

His Ser Ala Arg Met Ala Pro Met Leu Ala Glu Phe Ala Ala Glu Leu
180 185 190

Ala Gly Val Thr Trp Arg Glu Pro Glu Ile Pro Val Val Ser Asn Val
195 200 205

Thr Gly Arg Phe Ala Glu Pro Gly Glu Leu Thr Glu Pro Gly Tyr Trp
210 215 220

Ala Glu His Val Arg Arg Pro Val Arg Phe Ala Glu Gly Val Ala Ala
225 230 235 240

Ala Thr Glu Ser Gly Gly Ser Leu Phe Val Glu Leu Gly Pro Gly Ala
245 250 255

Ala Leu Thr Ala Leu Val Glu Glu Thr Ala Glu Val Thr Cys Val Ala
260 265 270

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Ala Leu Arg Asp Asp Arg Pro Glu Val Thr Ala Leu Ile Thr Ala Val
 275 280 285

Ala Glu Leu Phe Val Arg Gly Val Ala Val Asp Trp Pro Ala Leu Leu
 290 295 300

Pro Pro Val Thr Gly Phe Val Asp Leu Pro Lys Tyr Ala Phe Asp Gln
 305 310 315 320

Gln His Tyr Trp Leu Gln Pro Ala Ala Gln Ala Thr Asp Ala Ala Ser
 325 330 335

Leu Gly Gln Val Ala Ala Asp His Pro Leu Leu Gly Ala Val Val Arg
 340 345 350

Leu Pro Gln Ser Asp Gly Leu Val Phe Thr Ser Arg Leu Ser Leu Lys
 355 360 365

Ser His Pro Trp Leu Ala Asp His Val Ile Gly Gly Val Val Leu Val
 370 375 380

Ala Gly Thr Gly Leu Val Glu Leu Ala Val Arg Ala Gly Asp Glu Ala
 385 390 395 400

Gly Cys Pro Val Leu Glu Glu Leu Val Ile Glu Ala Pro Leu Val Val
 405 410 415

Pro Asp His Gly Gly Val Arg Ile Gln Val Val Val Gly Ala Pro Gly
 420 425 430

Glu Thr Gly Ser Arg Ala Val Glu Val Tyr Ser Leu Arg Glu Asp Ala
 435 440 445

Gly Ala Glu Val Trp Ala Arg His Ala Thr Gly Phe Leu Ala Ala Thr
 450 455 460

Pro Ser Gln His Lys Pro Phe Asp Phe Thr Ala Trp Pro Pro Pro Gly

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465	470	475	480
Val Glu Arg Val Asp Val Glu Asp Phe Tyr Asp Gly Phe Val Asp Arg			
	485	490	495
Gly Tyr Ala Tyr Gly Pro Ser Phe Arg Gly Leu Arg Ala Val Trp Arg			
	500	505	510
Arg Gly Asp Glu Val Phe Ala Glu Val Ala Leu Ala Glu Asp Asp Arg			
	515	520	525
Ala Asp Ala Ala Arg Phe Gly Ile His Pro Gly Leu Leu Asp Ala Ala			
	530	535	540
Leu His Ala Gly Met Ala Gly Ala Thr Thr Thr Glu Glu Pro Gly Arg			
545	550	555	560
Pro Val Leu Pro Phe Ala Trp Asn Gly Leu Val Leu His Ala Ala Gly			
	565	570	575
Ala Ser Ala Leu Arg Val Arg Leu Ala Pro Ser Gly Pro Asp Ala Leu			
	580	585	590
Ser Val Glu Ala Ala Asp Glu Ala Gly Gly Leu Val Val Thr Ala Asp			
	595	600	605
Ser Leu Val Ser Arg Pro Val Ser Ala Glu Gln Leu Gly Ala Ala Ala			
	610	615	620
Asn His Asp Ala Leu Phe Arg Val Glu Trp Thr Glu Ile Ser Ser Ala			
625	630	635	640
Gly Asp Val Pro Ala Asp His Val Glu Val Leu Glu Ala Val Gly Glu			
	645	650	655
Asp Pro Leu Glu Leu Thr Gly Arg Val Leu Glu Ala Val Gln Thr Trp			
	660	665	670

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Leu Ala Asp Ala Ala Asp Asp Ala Arg Leu Val Val Val Thr Arg Gly
675 680 685

Ala Val His Glu Val Thr Asp Pro Ala Gly Ala Ala Val Trp Gly Leu
690 695 700

Ile Arg Ala Ala Gln Ala Glu Asn Pro Asp Arg Ile Val Leu Leu Asp
705 710 715 720

Thr Asp Gly Glu Val Pro Leu Gly Arg Val Leu Ala Thr Gly Glu Pro
725 730 735

Gln Thr Ala Val Arg Gly Ala Thr Leu Phe Ala Pro Arg Leu Ala Arg
740 745 750

Ala Glu Ala Ala Glu Ala Pro Ala Val Thr Gly Gly Thr Val Leu Ile
755 760 765

Ser Gly Ala Gly Ser Leu Gly Ala Leu Thr Ala Arg His Leu Val Ala
770 775 780

Arg His Gly Val Arg Arg Leu Val Leu Val Ser Arg Arg Gly Pro Asp
785 790 795 800

Ala Asp Gly Met Ala Glu Leu Thr Ala Glu Leu Ile Ala Gln Gly Ala
805 810 815

Glu Val Ala Val Val Ala Cys Asp Leu Ala Asp Arg Asp Gln Val Arg
820 825 830

Val Leu Leu Ala Glu His Arg Pro Asn Ala Val Val His Thr Ala Gly
835 840 845

Val Leu Asp Asp Gly Val Phe Glu Ser Leu Thr Arg Glu Arg Leu Ala
850 855 860

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Lys Val Phe Ala Pro Lys Val Thr Ala Ala Asn His Leu Asp Glu Leu
 865 870 875 880

Thr Arg Glu Leu Asp Leu Arg Ala Phe Val Val Phe Ser Ser Ala Ser
 885 890 895

Gly Val Phe Gly Ser Ala Gly Gln Gly Asn Tyr Ala Ala Ala Asn Ala
 900 905 910

Tyr Leu Asp Ala Val Val Ala Asn Arg Arg Ala Ala Gly Leu Pro Gly
 915 920 925

Thr Ser Leu Ala Trp Gly Leu Trp Glu Gln Thr Asp Gly Met Thr Ala
 930 935 940

His Leu Gly Asp Ala Asp Gln Ala Arg Ala Ser Arg Gly Gly Val Leu
 945 950 955 960

Ala Ile Ser Pro Ala Glu Gly Met Glu Leu Phe Asp Ala Ala Pro Asp
 965 970 975

Gly Leu Val Val Pro Val Lys Leu Asp Leu Arg Lys Thr Arg Ala Gly
 980 985 990

Gly Thr Val Pro His Leu Leu Arg Gly Leu Val Arg Pro Gly Arg Gln
 995 1000 1005

Gln Ala Arg Pro Ala Ser Thr Val Asp Asn Gly Leu Ala Gly Arg Leu
 1010 1015 1020

Ala Gly Leu Ala Pro Ala Glu Gln Glu Ala Leu Leu Leu Asp Val Val
 1025 1030 1035 1040

Arg Thr Gln Val Ala Leu Val Leu Gly His Ala Gly Pro Glu Ala Val
 1045 1050 1055

Arg Ala Asp Thr Ala Phe Lys Asp Thr Gly Phe Asp Ser Leu Thr Ser

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1060	1065	1070
Val Glu Leu Arg Asn Arg Leu Arg Glu Ala Ser Gly Leu Lys Leu Pro		
1075	1080	1085
Ala Thr Leu Val Phe Asp Tyr Pro Thr Pro Val Ala Leu Ala Arg Tyr		
1090	1095	1100
Leu Arg Asp Glu Phe Gly Asp Thr Val Ala Thr Thr Pro Val Ala Thr		
1105	1110	1115
		1120
Ala Ala Ala Ala Asp Ala Gly Glu Pro Ile Ala Ile Val Gly Met Ala		
1125	1130	1135
Cys Arg Leu Pro Gly Gly Val Thr Asp Pro Glu Gly Leu Trp Arg Leu		
1140	1145	1150
Val Arg Asp Gly Leu Glu Gly Leu Ser Pro Phe Pro Glu Asp Arg Gly		
1155	1160	1165
Trp Asp Leu Glu Asn Leu Phe Asp Asp Asp Pro Asp Arg Ser Gly Thr		
1170	1175	1180
Thr Tyr Thr Ser Arg Gly Gly Phe Leu Asp Gly Ala Gly Leu Phe Asp		
1185	1190	1195
		1200
Ala Gly Phe Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro		
1205	1210	1215
Gln Gln Arg Leu Leu Leu Glu Ala Ala Trp Glu Ala Leu Glu Gly Thr		
1220	1225	1230
Gly Val Asp Pro Gly Ser Leu Lys Gly Ala Asp Val Gly Val Phe Ala		
1235	1240	1245
Gly Val Ser Asn Gln Gly Tyr Gly Met Gly Ala Asp Pro Ala Glu Leu		
1250	1255	1260

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Ala Gly Tyr Ala Ser Thr Ala Gly Ala Ser Ser Val Val Ser Gly Arg
1265 1270 1275 1280

Val Ser Tyr Val Phe Gly Phe Glu Gly Pro Ala Val Thr Ile Asp Thr
1285 1290 1295

Ala Cys Ser Ser Ser Leu Val Ala Met His Leu Ala Gly Gln Ala Leu
1300 1305 1310

Arg Gln Gly Glu Cys Ser Met Ala Leu Ala Gly Gly Val Thr Val Met
1315 1320 1325

Gly Thr Pro Gly Thr Phe Val Glu Phe Ala Lys Gln Arg Gly Leu Ala
1330 1335 1340

Gly Asp Gly Arg Cys Lys Ala Tyr Ala Glu Gly Ala Asp Gly Thr Gly
1345 1350 1355 1360

Trp Ala Glu Gly Val Gly Val Val Val Leu Glu Arg Leu Ser Val Ala
1365 1370 1375

Arg Glu Arg Gly His Arg Val Leu Ala Val Leu Arg Gly Ser Ala Val
1380 1385 1390

Asn Ser Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser
1395 1400 1405

Gln Gln Arg Val Ile Arg Arg Ala Leu Ala Gly Ala Gly Leu Glu Pro
1410 1415 1420

Ser Asp Val Asp Ile Val Glu Gly His Gly Thr Gly Thr Ala Leu Gly
1425 1430 1435 1440

Asp Pro Ile Glu Ala Gln Ala Leu Leu Ala Thr Tyr Gly Lys Asp Arg
1445 1450 1455

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Asp Pro Glu Thr Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Phe Gly
1460 1465 1470

His Thr Gln Ser Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Gln
1475 1480 1485

Ala Leu Arg His Gly Val Met Pro Pro Thr Leu His Val Asp Arg Pro
1490 1495 1500

Thr Ser Gln Val Asp Trp Ser Ala Gly Ala Val Glu Val Leu Thr Glu
1505 1510 1515 1520

Ala Arg Glu Trp Pro Arg Asn Gly Arg Pro Arg Arg Ala Gly Val Ser
1525 1530 1535

Ser Phe Gly Ile Ser Gly Thr Asn Ala His Leu Ile Ile Glu Glu Ala
1540 1545 1550

Pro Ala Glu Pro Gln Leu Ala Gly Pro Pro Pro Asp Gly Gly Val Val
1555 1560 1565

Pro Leu Val Val Ser Ala Arg Ser Pro Gly Ala Leu Ala Gly Gln Ala
1570 1575 1580

Arg Arg Leu Ala Thr Phe Leu Gly Asp Gly Pro Leu Ser Asp Val Ala
1585 1590 1595 1600

Gly Ala Leu Thr Ser Arg Ala Leu Phe Gly Glu Arg Ala Val Val Val
1605 1610 1615

Ala Asp Ser Ala Glu Glu Ala Arg Ala Gly Leu Gly Ala Leu Ala Arg
1620 1625 1630

Gly Glu Asp Ala Pro Gly Leu Val Arg Gly Arg Val Pro Ala Ser Gly
1635 1640 1645

Leu Pro Gly Lys Leu Val Trp Val Phe Pro Gly Gln Gly Thr Gln Trp

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1650	1655	1660	
Val Gly Met Gly Arg Glu Leu Leu Glu Glu Ser Pro Val Phe Ala Glu			
1665	1670	1675	1680
Arg Ile Ala Glu Cys Ala Ala Ala Leu Glu Pro Trp Ile Gly Trp Ser			
	1685	1690	1695
Leu Phe Asp Val Leu Arg Gly Asp Gly Asp Leu Asp Arg Val Asp Val			
	1700	1705	1710
Leu Gln Pro Ala Cys Phe Ala Val Met Val Gly Leu Ala Ala Val Trp			
	1715	1720	1725
Ser Ser Ala Gly Val Val Pro Asp Ala Val Leu Gly His Ser Gln Gly			
	1730	1735	1740
Glu Ile Ala Ala Ala Cys Val Ser Gly Ala Leu Ser Leu Glu Asp Ala			
1745	1750	1755	1760
Ala Lys Val Val Ala Leu Arg Ser Gln Ala Ile Ala Ala Lys Leu Ser			
	1765	1770	1775
Gly Arg Gly Gly Met Ala Ser Val Ala Leu Gly Glu Ala Asp Val Val			
	1780	1785	1790
Ser Arg Leu Ala Asp Gly Val Glu Val Ala Ala Val Asn Gly Pro Ala			
	1795	1800	1805
Ser Val Val Ile Ala Gly Asp Ala Gln Ala Leu Asp Glu Thr Leu Glu			
	1810	1815	1820
Ala Leu Ser Gly Ala Gly Ile Arg Ala Arg Arg Val Ala Val Asp Tyr			
1825	1830	1835	1840
Ala Ser His Thr Arg His Val Glu Asp Ile Glu Asp Thr Leu Ala Glu			
	1845	1850	1855

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Ala Leu Ala Gly Ile Asp Ala Arg Ala Pro Leu Val Pro Phe Leu Ser
 1860 1865 1870

Thr Leu Thr Gly Glu Trp Ile Arg Asp Glu Gly Val Val Asp Gly Gly
 1875 1880 1885

Tyr Trp Tyr
 1890

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 53789 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

GAATTCAGG CCGTCGACGG CTGCGACATC GCGGTCTTCC GGTGGTCGCA CCGCACGAAG	60
ATCGCCGAAT AAGAATTTCC GGATCTCCCA CGGGAAAGGT TTCCATGACC GACGCAATAT	120
CCTTCGAGGT GCCGTGGGAC CGGACCGACA AGTTCGACCC GCCCGCGGTG TTCGACTCTC	180
TGCGCGAAGA ACGTCCGCTC GCGAAGATGG TTTACCCGGA TGGGCACGTC GGCTGGATCG	240
TTTCCAGCTA CGAGCTGGTC CGCGAGGTCC TCAGCGACCT GCGGTTTCAGC CACAGCTGCG	300
AAGTCGGCCA CTTCCCGGTG ACCCACCAGG GCCAGGTCAT CCCGACCCAC CCGCTGATCC	360

CCGGCATGTT CATCCACATG GACCCGCCCC AGCACACGCG CTACCGCAAG CTGCTGACCG	420
GCGAGTTCAC CGTCCGCCGC GCCAGCAGGC TGATCCCCGC GGCCGAGGCC GTGGCCGCCG	480
AGCAGATCGA GGTTCATGCGG GCCAAGGGCG CCCCCGCGGA CGTGGTCATG GACTTCGCCA	540
AGCCGCTGGT GCTGCGGATG CTGGGCGAGC TCGTCGGCCT GCCCTACGAG GAACGCGACC	600
GGTACGTGCC CGCGGTGACC CTCCTGCACG ACGCCGAAGC GGACCCGGCC GAGGCCGCGG	660
CCGCCTACGA GGTGGCCGGG AAGTTCTTCG ACGAGGTCAT CGAGCGCCGC CGGCAGCGGC	720
CCCAGGACGA CCTCATCAGC TCGCTCGTCA CCGAGGACCT GACCCAGGAG GAGCTGCGCA	780
ACATCGTCAC CCTGCTGCTG TTCGCCGGGT ACGAGACCAC CGAGGGCGCG CTCGCCACCG	840
GCGTCTTCGC GCTGCTGCAC CACACCGATC AGCTGGCGGC ACTGCGCGCG GAGCCGGAAA	900
AGCTCGACGC CGCGATCGAA GAGCTGCTGC GCTACCTGAC CGTCAACCAG TACCACACCT	960
ACCGCACCGC GCTGGAGGAC GTGAAGCTGG AGGGCGAGCT GATCAAGAAG GCGGACACGG	1020
TGACGGTGTC GCTGCCCCGC GCCAACCGCG ACCCGGCCAA GTTCGGCTGT CCCGCGGAGC	1080
TCGACATCGA GCGGGACACC TCCGGCCACG TCGCGTTCGG CTTCCGGCATC CACCAGTGCC	1140
TGGGCCAGAA CCTGGCGCGC ATCGAGCTGC GGGCCGGCTT CACGGCGCTC CTGCGGGCGT	1200
TCCCCGAGCT CCGGCTGGCC GTCCCGGCCG ACGAGGTTCC GCTGCGGCTG AAGGGTTCCG	1260
TCTTCTCGGT GAAGAAGCTG CCCGTCTCCT GGTGAGCGTT CTTCCCCTCG AACACCCGAA	1320
AGGATCTGCG GCACAGTGCG CACCGATCTC ATCAAGCCAC TTCACGTGCG ACTCCTGGAG	1380
AACGCGACCC GCTTCGCCGG CAAGCCGGCC TTCGCCGACG ACCACCGGAC GGTACCTAC	1440
GGCGACCTCG AGGCGCGGAC GCGCCGGCTG GCCGGGCACC TGGCCGGCCT CGGTGTCCGG	1500

CACGGCGACC GGGTGGCGAT CTGCCTCGGC AACCGGGTGT CCACTGTGGA GAGTTACTTC	1560
GCGATCCTGC GCGCGGGTGC CGTCGGCGTG CCGCTCAACC CCGGTTCGGC GACGGCCGAG	1620
CTCGAGCACC CGCTGACCGA CAGCGGCGCC ACGGTGGTCG TCACCGACGC CGCCCAGGCG	1680
GCCCGGCTCC GGCTCGCGCC GCACGTCGAG CTGCTGGTGA CCGGCGACGA CGTCCCGGAG	1740
GGCGCCCACT CCTACGACGA ACTCGCCCTC AGCGAACCGG CCGAGCCCGC CGCGGACGAC	1800
CTCGAGCTCG ACGAGCCGGC GTGGATGTTT TACACGTCGG GCACGACCGG GCGGCCAAG	1860
GGCGTCGTGT CCACGCAGCG CAACTGCCTC TGGTCCGTCT CTTCCTGCTA CGTGCCGTTC	1920
CCCGGGTTGT CGGACCAGGA CCGGGTGCTC TGGCCGCTCC CGCTGTTCCA CAGCCTTTTCG	1980
CACATCGCCT GCGTCCTGTC CGCCACCGTG GTCGGGGCCA GCGTCCGGAT CGCCGACGGC	2040
AGCTCCGCCG ACGACGTGAT GCGGCTGATC GAGGCGGAGA GCTCGACCTT CCTGGCCGGC	2100
GTGCCGACCA CCTACCACCA CCTGGTGCGG GCCGCCCGGC AGCGCGGTTT CTCCGCGCCG	2160
AGCCTGCGGA TCGGCCTGGC CGGGGGCGCG GTCCTCGGCG CCGGGCTGCG AAGCGAGTTC	2220
GAAGAGACCT TCGGGGTCCC GCTGATCGAC GCCTACGGCA GCACCGAGAC CTGCGGGGCG	2280
ATCACCATGA ACCCGCCGGA CGGCGCCCGC GTCGAGGGCT CGTGCGGCTT GGCCGTGCCG	2340
GGCGTCGACG TCGGGGTCTG CGACCCCGAC ACCGGGCTCG ACGTCCCCGC CGGCGAGGAG	2400
GGCGAGGTCT GGGTCAGCGG GCCGAACGTC ATGCTCGGCT ACCACAACAG CCCGGAGGCG	2460
ACCGCCGCGG CGATCGGGGA CGGCTGGTTC CGGACCGGGG ACCTGGCCCG CCGCGACGAC	2520
GCCGGTTACT TCACCATCTG CGGCCGGATC AAGGAACTCA TCATCCGCGG CGGCGCGAAC	2580

ATCCACCCCG GCGAGGTCTGA GCGGGTCCTG CGCACGGTCG ACGGCGTCGC GGACGCGGCG	2640
GTCGGCGGTG TGCCGCACGA CACGCTCGGC GAGGTGCCGG TCGCTACGT CATCCCCGGA	2700
CCGACCGGTT TCGATCCTGC GCGGTTGATC GAGAAGTGCC GCGAACAGCT GTCCGCCTAC	2760
AAGGTGCCGG ACCGGATCCT CGAGGTGCGC CACATTCCCC GGACCGCGTC GGGCAAGATC	2820
CGGCGCGGGC TGCTGACCGA CGAGCCCGCG CAGCTGCGGT ACGCCGCGAC CGAACACGAG	2880
GAACAGTCCC GGCACGCCGA CGAGTCCGTC GCGGCGGGCG TGCGCGCGCG ACTGTCCGGT	2940
TTGGACGAAC GCGCCCAGTG CGAGCTCCTG GAAGACCTCG TCCGCACCCA GGCGGCCGAC	3000
GTGCTGGGGC AGCCGGTCCC GGACGGGCGT GCGTTCCGCG ACCTCGGCTT CACGTCGCTG	3060
GCCATCGTGG AGCTGCGCAA CCGGCTGACC GAGCACACCG GGCTCTGGCT GCCCGCCAGC	3120
GCCGTCTTCG ACCACCCAC GCCGGCGGCG CTGGCCGCCC GCGTCCGGGC TGAGCTCCTC	3180
GGGATCACGC AGGCCGTGCG GGAGCCGGTC GTCGCGGCCG ACCCGGGCGA GCCGATCGCG	3240
ATCGTGGGGA TGGCTGCCG CCTGCCGGGT GCGGTGGCGT CCCCGAAGA CCTGTGCGCG	3300
CTGGTGGCCG AGCGCGTCGA CGCCGTTTCG GAGTTCCCCG GCGACCGCG CTGGGACCTG	3360
GACAGCCTGA TCGACCCGGA CCGGGAGCGC GCCGGGACGT CGTACGTCGG CCAGGGCGGA	3420
TTCTGACAG ACGCCGGCGA GTTCGACGCC GGGTTCTTCG GGATCTCGCC GCGTGAGGCC	3480
GTCGCGATGG ACCCGCAGCA GCGGTTGCTG CTGGAGACGT CGTGGGAGGC CCTCGAAAAC	3540
GCCGGAGTCG ACCCGATCGC GTTGAAGGGC ACCGACACCG GCGTGTTCCTC CGGCCTCATG	3600
GGCCAGGGGT ACGGGTCCGG CGCGGTGGCG CCGGAGCTCG AAGGTTTCGT CACCACCGGG	3660
GTCGCGTCGA GCGTGGCCTC GGGCCGGGTG TCGTACGTGC TGGGACTGGA AGGCCCCGGC	3720

GTCACCGTGG ACACCGCGTG TTCGTCGTCG CTGGTCGCGA TGCACCTGGC CGCGCAGGCC 3780

CTGCGGCAGG GCGAATGCTC GATGGCGCTC GCCGGCGGGG TCACGGTGAT GGCCACGCCG 3840

GGCTCGTTCG TCGAGTTCTC CCGCCAGCGG GCCCTGGCGC CCGACGGGCG CTGCAAGGCC 3900

TTCGCGGCGG CGGCCGACGG GACCGGCTGG TCCGAGGGTG TCGGCGTGGT CGTCCTCGAG 3960

CGGCTGTCCG TGGCGCGCGA GCGGGGCCAC CGGATCCTGG CCGTTTTCG TGGCAGCGCG 4020

GTCAACCAGG ACGGCGCGTC CAACGGGCTC ACCGCGCCGA ACGGCCTCTC GCAGCAGCGG 4080

GTCATCCGCC GCGCGCTGGC CGCGGCCGGG CTGGCACCGT CCGATGTGGA CGTCGTCGAG 4140

GCGCACGGCA CCGGGACCAC GCTGGGTGAC CCGATCGAGG CGCAGGCCCT GCTGGCGACC 4200

TACGGCCAGG AGCGGAAGCA GCCGTTGTGG CTCGTTTCGC TCAAGTCGAA CATCGGCCAC 4260

GCGCAGGCGG CCGCGGGCGT TCGGGGCGTC ATCAAGATGG TGCAGGCGCT GCGGCACGAG 4320

ACCTTGCCGC CGACGCTGCA TGTCGACAAG CCGACTCTTG AGGTGGACTG GTCCGCCGGT 4380

GCCATTGAAC TGCTGACGGA GGCCCGTGCG TGGCCGCGCA ACGGCCGTCC GCGCCGGGCC 4440

GGGTGTCTGT CGTTCGGCGT CAGCGGGACC AACGCGCACC TGATCCTGGA GGAGGCGCCG 4500

GCCGAGGAGC CGGTGCTGC CCCGGAAGTG CCGGTGGTGC CCCTGGTGGT GTCGGCGCGG 4560

AGCACGGAGT CGCTGTCCGG GCAGGCCGAG CGGCTGGCGT CCCTCCTCGA AGGGGACGTC 4620

TCGCTGACCG AGGTGGCCGG GCGCTGGTG TCCCGCCGGG CGGTGCTGGA CGAGCGGGCC 4680

GTCGTCGTGG CCGGTTTCGCG CGAGGAAGCC GTGACGGGC TCGGGGCGCT GAACACGGCC 4740

GSTTCGGGGA CGCCGGGCAA GGTGCTGTGG GTGTTCCCGG GGCAGGGGAC GCAGTGGGCC 4800

GGGATGGGCC GTGAGCTGCT GGCCGAGTCC CCGGTGTTTCG CCGAGCGGAT CGCCGAGTGC	4860
GCGGCCGCGT TGGCGCCGTG GATCGACTGG TCGCTCGTCG ACGTCCTGCG CGGCGAGGGC	4920
GACCTGGGTC GGGTCGATGT GCTGCAGCCG GCCTGTTTCG CCGTGATGGT CGGGCTGGCT	4980
GCCGTCTGGG AGTCCGTGGG GGTCCGGCCG GACGCCGTCTG TCGGGCACTC GCAGGGTGAG	5040
ATCGCGGCTG CCTGCGTTTC GGGGGCGTTG TCCCTCGAGG ACGCGGCGAA GGTGGTG GCC	5100
CTGCGCAGCC AGGCCATCGC GCGGGAAC TG TCCGGCCGCG GCGGGATGGC GTCGGTCGCC	5160
CTGGGCGAGG ACGACGTCGT TTCGCGGCTG GTGGACGGGG TCGAGGTCGC CGCCGTCAAC	5220
GGCCCGTCGT CCGTGGTGAT CGCCGGGGAT GCCCATGCCC TCGACGCGAC CCTGGAAATC	5280
TTGTCCGGGG AAGGCATCCG GGTTCGGCGG GTGGCGGTGG ACTACGCCTC GCACACCCGG	5340
CATGTCGAGG ACATCCGCGA CACTCTTGCC GAAACCTTGG CCGGGATCAG TGCGCAGGCG	5400
CCGGCTGTGC CGTTCTACTC CACCGTCACG AGCGAGTGGG TGCGCGACGC GGGGGTGCTG	5460
GACGGCGGCT ACTGGTACCG GAACCTGCGC AACCAGGTCC GGTTCGGAGC GGCCGCGACG	5520
GCCCTGCTCG AGCAGGGCCA CACGGTGTTT GTCGAGGTCA GTGCGCACCC GGTGACGGTC	5580
CAGCCCTTGA GCGAGCTCAC CGGGGACGCG ATCGGGACAT TCGGGCGTGA AGACGGTGCC	5640
CTGCGGCGGT TGCTGGCTTC GATGGGTGAG CTGTTCTGTC GCGGCATCGA CGTGGACTGG	5700
ACGGCGATGG TGCCCGCGGC CGGCTGGGTC GACTTGCCGA CCTACGCGTT CGAACACCGG	5760
CACTACTGGC TCGAGCCCGC CGAGCCCGCT TCGGCCGAG ACCCGCTGCT GGGCACAGTC	5820
GTCAGCACTC CCGTTTCGGA CCGACTCACC GCCGTGGCGC AGTGGTCGCG CCGGGCGCAG	5880
CCCTGGGCGG TGGACGGCCT GGTGCCGAAC GCGGCCCTGG TCGAGGCGGC CATCCGGCTC	5940

GGCGACCTGG CCGGCACCCC CGTCGTCGGC GAACTGGTCG TCGACGCGCC GGTGGTGCTG	6000
CCGCGGCGCG GCAGCCGCGA GGTCCAGCTG ATCGTCGGCG AGCCCGGCGA GCAGCGGCGG	6060
CGTCCGATCG AGGTCTTTTC CCGGGAAGCC GACGAGCCGT GGACGCGGCA CGCGCACGGC	6120
AACTCGCTC CCGCCGCCGC TCGGTGCCA GAACCGGCGG CGGCGGGAGA CGCCACCGAC	6180
GTCACCGTGG CCGGCCTGCG CGACGCGGAC CGGTACGGGA TCCACCCCGC GCTGCTGGAC	6240
GCCGCCGTCC GCACGGTCGT CGGCGACGAC CTGCTCCCGT CGGTGTGGAC CGGCGTGTC	6300
CTGCTGGCCT CCGGGGCCAC GGCCGTGACC GTGACGCCGA CGGCGACCGG CCTGCGGCTG	6360
ACCGACCCGG CCGGGCAGCC CGTCCTGACC GTCGAATCCG TCGCGGCAC GCCGTTCTGTC	6420
GCCGAGCAGG GGACCACCGA CGCGCTCTTC CGCGTCGACT GGCCGAAAT CCCGCTGCCC	6480
ACCGCCGAAA CCGCGGACTT CCTGCCGTAC GAAGCCACGT CGGCCGAGGC GACCCTCTCC	6540
GCGCTCCAGG CCTGGCTGGC AGACCCCGCG GAAACCCGGC TGGCCGTGGT CACCGGGGAC	6600
TGCACCGAAC CCGGCGCGGC CGCGATCTGG GGCCTGGTGC GCTCGGCGCA GTCCGAACAC	6660
CCCGGCCGGA TCGTGCTGGC CGACCTCGAC GACCCCGCG TGTGCCCCG CGTGGTGCGG	6720
AGCGGCGAAC CGCAGGTGCG GGTGCGCAAC GGCCTCGCCT CGGTGCCGCG CTTGACCCGG	6780
GTTACTCCCC GGCAGGACGC GCGGCCGCTC GACCCCGAGG GCACCGTCCT GATCACCGGC	6840
GGCACCGGCA CGCTCGGTGC GCTGACCGCC CGGCACCTCG TCACCGCGCA CGGCGTCCGG	6900
CACCTGGTGC TGGTCAGCCG CCGCGGTGAG GCTCCCAGC TGCAGGAAGA ACTGACCGCA	6960
CTGGGGGCAT CCGTCGCCAT CGCCGCTGC GACGTGGCAG ACCGGGCGCA GCTCGAAGCC	7020

GTCTTGCGCG CGATCCCGGC CGAGCACCCG CTCACCGCCG TGATCCACAC CGCGGGGGTC	7080
CTCGACGACG GCGTCGTCAC CGAGCTGACC CCGGACCGGC TCGCCACCGT GCGGCGGGCCG	7140
AAGGTCGACG CCGCCCGGCT CCTGGACGAG CTCACCCGGG AGGCCGATCT CGCCGCGTTC	7200
GTGCTGTTCT CCTCGGCGGC GGGTGTGCTG GGCAACCCCG GCCAGGCCGG GTACGCCGCC	7260
GCCAACGCCG AGCTGGATGC GTTGGCGCGC CAGCGGAACA GCCTCGACCT GCCCGCGGTG	7320
TCCATCGCAT GGGGCTACTG GGCGACGGTC AGCGGGATGA CCGAGCACCT GGGCGACGCC	7380
GACCTGCGGC GCAACCAGCG GATCGGCATG TCCGGGCTTC CCGCCGACGA GGGCATGGCG	7440
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ACCGGCCGGG	TGCTGGCCGC	CCTGCAGGCG	TGGCTTTCCG	ACGCGGCGGA	GGAAGCCCGC	34500
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GGTGCCGCGG	TGTGGGGCCT	GGTCCGGGCC	GCGCAGGCGG	AGAACCCGGA	CCGGTTCGTC	34620
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GGCCTGAAAC	TGCCCCGCGAC	GCTGGTCTTC	GACCATCCGA	ACCCGCTGGC	ACTGGCCCCG	35820
CACCTGCGGG	CGGAACTCGC	CGTCGACGAG	GCATCCCCGG	CCGATGCGGT	GCTGGCCGGG	35880

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TTTCCGACGT	CGCCGGTGCG	CTGACGAGCC	GCGCCCTGTT	CGGCGAGCGC	GCGGTCTGTC	47940
TGGCGGATTC	GGCCGAGGAA	GCCCAGCGCC	GTCTGGGCGC	ACTGGCCCGC	GGCGAAGACG	48000
CGCCGGGCCCT	GGTCCGCGGC	CGGGTGCCCG	CGTCCGGCCT	GCCGGGCAAG	CTCGTGTGGG	48060
TGTTCCCCGG	GCAGGGGACG	CAGTGGGTGG	GCATGGGCCG	CGAACTCCTC	GAAGAGTCTC	48120

CGGTGTTTCG CGAGCGGATC GCCGAGTGTG CGGCCGCGCT GGAGCCGTGG ATCGGCTGGT 48180

CGCTGTTTGA CGTCCTCCGT GCGACGGTG ACCTCGATCG GGTGATGTG CTGCAGCCCC 48240

CGTGCTTTGC GGTGATGGTC GGCTTGGCCG CGGTGTGGTC CTCGGCCGGG GTGGTCCCCG 48300

ATGCGGTGCT CGGCCACTCC CAGGGTGAGA TCGCCCGGGC GTGCGTGTG GGTGCGTTGT 48360

CGCTGGAGGA TGCGGCGAAG GTGGTTGCCC TGCGCAGCCA GGCCATCGCC GCGAAGCTCT 48420

CCGGCCCGCG CGGGATGECT TCGGTCGCCT TGGGCGAAGC CGATGTGGTG TCGCGGCTGG 48480

CGGACGGGGT CGAGGTGGCT GCCGTCAACG GTCCGGCGTC CGTGGTGATC GCGGGGGATG 48540

CCCAGGCCCT CGACGAAACG CTGGAAGCGC TGTCCGGTGC GGAATCCGG GCTCGGCGGG 48600

TGGCGGTGGA CTACGCCTCG CACACCCGGC ACGTCAAGA CATCGAAGAC ACCCTCGCCG 48660

AAGCGCTGGC CGGGATCGAC GCCCGGGCGC CGCTGGTGCC GTTCCTCTCC ACCCTCACCG 48720

GCGAGTGGAT CCGGGACGAG GCGTTCGTGG ACGGCGGCTA CTGGTACCGG AACCTGCGCG 48780

GCCGGGTGCG GTTCGGCCCG GCCGTCGAGG CGCTGCTGGC CCAGGGGCAC GGTGTGTTTCG 48840

TCGAGCTCAG CGCCCACCG GTGCTGGTCC AGCCGATCAC CGAGCTCACC GACGAAACCG 48900

CCGCCGTCGT CACCGGTTTCG CTGCGCCGGG ACGACGGTGG CCTGCGCCGG CTGCTGACCT 48960

CGATGSCCGA GCTCTTCGTC CGTGGGGTCG AAGTGGACTG GACGTCGCTG GTGCCGCCGG 49020

CCCGGGCCGA CCTCCCGACG TACGCCTTCG ACCACGAGCA CTACTGGCTC CGCGCCGCGG 49080

ACACCGCTTC CGACGCCGTC TCGCTGGGGC TGGCCGGGGC GGACCACCCG CTGCTCGGCG 49140

CGGTCGTGCA GCTTCCGCAG TCCGACGGCC TGGTCTTCAC TTCCCGGCTC TCCCTGCGCT 49200

CGCACCCCTG GCTGGCCGAC CACGCGGTCC GGGACGTCGT GATCGTCCCC GGCACCGGGC 49260

TGGTCGAGCT GGCCGTGCGG GCCGGTGACG AAGCCGGCTG CCCGGTGCTC GACGAGCTGG 49320

TGATCGAGGC GCCGCTCGTG GTGCCCCGCC GCGGCGGGGT CCGCGTGACG GTCGCCCTCG 49380

GCGGCCCCGC CGACGACGGT TCGCGCACGG TGGACGTCTT CTCCCTGCGC GAAGACGCGG 49440

ACAGCTGGCT CCGGCACGCC ACGGGCGTGC TGGTCCCGGA GAACCGGCCG CGGGGGACCG 49500

CCGCGTTCGA CTTGCGCCGCC TGGCCGCCAC CGGAGGCGAA GCCCGTGGAC CTCACCGGTG 49560

CCTACGACGT GCTCGCGGAC GTCGGGTACG GCTACGGGCC CACGTTCCGG GCCGTGCGGG 49620

CCGTGTGGCG GCGCGGCAGC GGGAAACACCA CCGAGACCTT CGCCGAGATC GCCCTGCCCC 49680

AAGACGCCCC CGCGGAAGCC GGCCGGTTCG GCATCCACCC CGCGCTGCTG GACGCGGCCC 49740

TGCACTCGAC GATGGTCAGC GCCGCGGCGG ACACCGAGTC CTACGGCGAC GAAGTGCGGC 49800

TGCCGTTCGC GTGGAACGCG CTGCGGCTGC ACGCGGCCGG CGCCTCGGTG CTGCGGGTGC 49860

GCGTCGCCAA GCCCGAGCGG GACAGTCTGT CGCTCGAGGC CGTCGACGAG TCCGGCGGCC 49920

TGGTCGTGAC GCTGGATTCC CTGGTCGGGC GCCCGGTGTC GAACGACCAG CTGACGACGG 49980

CGGCGGGGCC GCGGGCGGCC GGCTCGCTGT ACCGCGTGGA CTGGACGCCA TTGTCCTCAG 50040

TGGACACTTC GGGACGGGTG CCGTCCTGGC TTCCGGTTCG CACCGCGGAA GAGGTGGCGA 50100

CGCTGGCCGA CGACGTCCTG ACCGGCGCGA CCGAGGCGCC GGCGGTGGCC GTCATGGAGG 50160

CCGTCGCCGA CGAGGGTTC GTGCTGGCGC TCACCGTCCG GGTGCTGGAC GTGCTCCAGT 50220

GCTGGCTGGC CGGCGGCGGG CTGGAGGGGA CGAAGCTCGC GATCGTGACC CGCGGCGCGG 50280

TGCCCCCGCG CGACGGCGTG GTGCACGACC CGGCCCGCGC CGCGGTGTGG GGGCTGGTCC 50340

GGGCCGCGCA GCGGAGAAC CCGGACCGGA TCGTCTCTCT CGACGTCGAG CCGGAAGCCG 50400

ACGTACCGCC GCTGCTGGGT TCGGTGCTCG CCGACGGCGA GCCGCAGGTC GCGGTGCGCG 50460

GAACCACGCT GTCCATCCCC CGCCTCGCCC GCGCCGCCCG GCCCGACCCG GCCGCCGGGT 50520

TCAAGACCCG GGGACCGGTG CTGGTCACCG GCGGGACCGG GTCGCTCGGC GGCCTGGTCG 50580

CCCGGCACCT GGTGAGCGG CACGGCGTCC GGCAGCTGGT GCTGGCGAGT CGCCGGGGCC 50640

TGGACGCCGA AGGCGCGAAG GACCTGGTCA CCGACCTCAC CGCACTGGGG GCCGACGTCG 50700

CGGTGCGCCG TTGCGACGTC GCCGACCGGG ACCAGGTGGC GGCCCTGCTG ACCGAGCACC 50760

GGCCGTCCGC CGTGGTGCAC ACGGCCGGCG TCCCGGACGC CGGGGTGATC GGGACGGTGA 50820

CCCCGGACCG GCTGGCCGAG GTGTTGCGC CCAAGGTCAC CGCGGCCCGG CACCTCGACG 50880

AGCTGACCCG CGACCTGGAC CTCGACAGTT TCGTCGTCTA CTCCTCGGTT TCCGCGGTGT 50940

TCATGGGCGC CGGCAGCGGC AGCTACGCCG CGGCGAACGC GTACCTGGAC GGGCTGATGG 51000

CCCACCGGCG CGCGCCCGGC CTGCCGGGCC AGTCGCTGGC GTGGGGGCTG TGGGACCAGA 51060

CCACCGGCGG CATGGCGGCC GGGACCGACG AGGCCGGCCG GGCCCGGATG ACCCGCGCG 51120

GCGGCCTGGT CGCGATGAAA CCCGCCGCCG GACTGGACCT CTTCGACGCT GCCATCGGGT 51180

CCGGCGAGCC GCTGCTGGTG CCCGCCAGC TCGACCTGCG GGGCCTGCGC GCCGAAGCGG 51240

CGGGCGGCAC CGAAGTGCCG CACCTGCTGC GCGGCCTGGT CCGCGCCGGA CGCCAGCAGG 51300

CCCGTGCGGC GTCCACTGTG GAGGAGAACT GGGCCGGCCG GCTGGCCGGG CTCGAGCCCG 51360

CCGAGCGGGG CCAGGTCTCT CTGGAAC TGGCGGCCCA GGTGGCAGG GTCTTGGGCT 51420

ACCGCGCCGC	CCACCAGGTC	GACCCGGACC	AGGGCCTGTT	CGAGATCGGG	TTCGACTCGC	51480
TCACCGCGAT	CGAACTCCGC	AACCGGCTGC	GCGCCAGGAC	CGAACGGAAG	ATCTCGCCCG	51540
GTGTCGTCTT	CGACCATCCC	ACGCCGGCCC	TGCTCGCCGC	GCACTTGAAC	GAGCTGCTCC	51600
GAAAGAAGGT	GTGAACGTGT	TCGACGTGGA	GACCTACCTC	CAGCGGATCG	GCTGCGGCGG	51660
GGAAACCGGC	GTGGACCTCG	AAACGCTGGC	GAAGCTGCAG	AAGAGCCACC	TGATGGCGAT	51720
CCCGTACAGC	AGCCTCGCCT	ACGAACTCCG	GGACGCGGTG	AACGTCGTCG	ACCTCGACGA	51780
GGACGACGTC	TTCGTCACCA	GCATCGCCGA	AGGGCAGGGC	GGCGCCTGCT	ACCACCTGAA	51840
CCGGCTGTTC	CACCGGCTCC	TGACCGAACT	CGGCTACGAC	GTCACGCCGC	TGGCCGGCAG	51900
CACCGCCGAA	GGCCGGGAGA	CCTTCGGCAC	CGACGTCGAG	CACATGTTCA	ACCTGGTCAC	51960
CCTGGACGGC	GCCGACTGGC	TCGTGGACGT	CGGCTACCCC	GGCCCCACCT	ACGTCGAGCC	52020
ACTGGCGGTC	TGCCCCGCGG	TGCAGACCCA	GTACGGGAGC	CAGTTCCGGT	TGGTGGAACA	52080
GGAAACCGGT	TATGCGCTGC	AACGCCGGGG	TGCGGTCACC	CGCTGGAGCG	TCGTCTACAC	52140
GTTACGACG	CAACCGCGTC	AGTGGAGTGA	CTGGAAGGAA	CTGGAGGACA	ACTTCCGGGC	52200
CCTCGTGGGG	GACACCACCC	GCACCGACAC	GCAGGAAACC	CTGTGCGGCC	GCGCGTTCGC	52260
GAACGGCCAG	GTCTTCCTGC	GGCAGCGCCG	CTACCTGACG	GTCGAGAACG	GCCGCGAGCA	52320
GGTGCGCACG	ATCACCGACG	ACGACGAGTT	CCGGGCGCTG	GTGTCCCGCG	TGCTGTCCGG	52380
CGACCACGGC	TGAACTGGCG	AAAGGCACGA	CGATGACGGA	AAAAGCGGGC	CTGCTGGCGA	52440
AGTTCGCCCG	CCTCTGCAAA	ACCGCCTACG	AGCACCCTA	CATCCCGTAC	CTGCACTTCT	52500
TCTACGGCGG	CGAGTACCTC	CACCACGGCA	GCGAGCCGGT	GTCCCGGATC	GCGGACCTGC	52560

CGTACGTGAC	CGTGCCGGAG	CCGCGGAAGA	AGGCGCCGTG	AGGACGACGA	TCCCAGGTCCG	52620
CCTGGCGGAA	CGGTCTTACG	ACGTGCTCGT	CGGCCCCGGG	GTGCGGGCGG	CGCTGCCCCGA	52680
GGTCGTCCGG	CGGCTCGGCG	CGAGACGGGC	CGTGGTCGTG	TCGGCCCCGGC	CGGCGGACTG	52740
GGTGCCCCGGC	ACCGGCGTCG	AGACCCTGCT	GCTCCAGGCG	CGCGACGGCG	AGCCGACCAA	52800
GCGGCTGTCC	ACAGTGGAGG	AACTGTGCGG	TGAGTTCGCG	CGGTTGCGGC	TCACCCGGTC	52860
CGACGTCTGTG	GTCTCTTGCG	GCGGCGGCAC	GACCACGGAC	GTCGTGCGGC	TCGCGGCCGC	52920
GCTGTACCAC	CGGGGGGTCTG	CCGTGGTCCA	CCTGCCCCACG	TCCCTGCTCG	CCCAGGTCTGA	52980
CGCCAGCGTC	GGCGGGAAGA	CCGCGGTGAA	CCTGCCGGCG	GGCAAGAACC	TCGTGCGGGC	53040
GTA CTGGCAG	CCCAGCGCGG	TGCTGTGCGA	CACGGACTAC	CTGACGACGC	TGCCGCGGCG	53100
GGAGGTGCTG	AACGGCCTCG	GCGAGATCGC	CCGCTGCCAC	TTCATCGGCG	CGCCGGACCT	53160
GCGGGGGCGC	TCGCGCCCCG	AGCAGATCGC	CGCCAGCGTC	ACCCTCAAGG	CGGGCATCGT	53220
CGCGCAGGAC	GAGCGGGACA	CCGGCCCCGG	GCACCTGCTC	AACTACGGCC	ACACGCTGGG	53280
GCACGCGCTG	GAGATCGCGA	CCGGCTTCGC	CCTGCGCCAC	GGCGAGGCGG	TGGCGATCGG	53340
CACGGTCTTC	GCGGGCCGGC	TGGCCGGCGC	GCTCGGCCGC	CTCGACCAGT	CCGGTGTGGA	53400
CGAACACCTC	GCCGTCTGTC	GCCACTACGG	CCTGCCCCGC	GCGCTGCCCG	CGGACGTCTGA	53460
CCCGCGGGTG	CTCGTCCGGC	AGATGTACCG	GGACAAGAAG	GCGATCACCG	GGCTCGCCTT	53520
CGTCCTGGCC	GGGCCGCGGG	GCGCGGAGCT	GGTGAGCGAC	GTGCCGGCGC	CGGTCTGTAC	53580
CGACGTCTTG	GACCGGATGC	CCC CGACAG	CCTGGAAAAC	CTGGTGGGGA	CGACGGAAGC	53640

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GGCGGCGCCG TGAAGCGGCA GCCGGACTTC GCGGCCACG GCCGGGCGGT CGACCGGGTG 53700

CTGGCCGGCC GGCTGAGCGC GGCCTGGCC CGGCCGGCCG CGCAGCAGCC GGGCTGGCCG 53760

GACGCCGAGC GGGCGGCCGA GGTGAATTC 53789

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4572 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Met Phe Tyr Thr Ser Gly Thr Thr Gly Arg Pro Lys Gly Val Val Ser
1 5 10 15

Thr Gln Arg Asn Cys Leu Trp Ser Val Ala Ser Cys Tyr Val Pro Phe
20 25 30

Pro Gly Leu Ser Asp Gln Asp Arg Val Leu Trp Pro Leu Pro Leu Phe
35 40 45

His Ser Leu Ser His Ile Ala Cys Val Leu Ser Ala Thr Val Val Gly
50 55 60

Ala Ser Val Arg Ile Ala Asp Gly Ser Ser Ala Asp Asp Val Met Arg
65 70 75 80

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Val Gly Gly Val Pro His Asp Thr Leu Gly Glu Val Pro Val Ala Tyr
275 280 285

Val Ile Pro Gly Pro Thr Gly Phe Asp Pro Ala Ala Leu Ile Glu Lys
290 295 300

Cys Arg Glu Gln Leu Ser Ala Tyr Lys Val Pro Asp Arg Ile Leu Glu
305 310 315 320

Val Ala His Ile Pro Arg Thr Ala Ser Gly Lys Ile Arg Arg Gly Leu
325 330 335

Leu Thr Asp Glu Pro Ala Gln Leu Arg Tyr Ala Ala Thr Glu His Glu
340 345 350

Glu Gln Ser Arg His Ala Asp Glu Ser Val Ala Ala Ala Leu Arg Ala
355 360 365

Arg Leu Ser Gly Leu Asp Glu Arg Ala Gln Cys Glu Leu Leu Glu Asp
370 375 380

Leu Val Arg Thr Gln Ala Ala Asp Val Leu Gly Gln Pro Val Pro Asp
385 390 395 400

Gly Arg Ala Phe Arg Asp Leu Gly Phe Thr Ser Leu Ala Ile Val Glu
405 410 415

Leu Arg Asn Arg Leu Thr Glu His Thr Gly Leu Trp Leu Pro Ala Ser
420 425 430

Ala Val Phe Asp His Pro Thr Pro Ala Ala Leu Ala Ala Arg Val Arg
435 440 445

Ala Glu Leu Leu Gly Ile Thr Gln Ala Val Ala Glu Pro Val Val Ala
450 455 460

Ala Asp Pro Gly Glu Pro Ile Ala Ile Val Gly Met Ala Cys Arg Leu

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465	470	475	480
Pro Gly Gly Val Ala Ser Pro Glu Asp Leu Trp Arg Leu Val Ala Glu			
	485	490	495
Arg Val Asp Ala Val Ser Glu Phe Pro Gly Asp Arg Gly Trp Asp Leu			
	500	505	510
Asp Ser Leu Ile Asp Pro Asp Arg Glu Arg Ala Gly Thr Ser Tyr Val			
	515	520	525
Gly Gln Gly Gly Phe Leu His Asp Ala Gly Glu Phe Asp Ala Gly Phe			
	530	535	540
Phe Gly Ile Ser Pro Arg Glu Ala Val Ala Met Asp Pro Gln Gln Arg			
545	550	555	560
Leu Leu Leu Glu Thr Ser Trp Glu Ala Leu Glu Asn Ala Gly Val Asp			
	565	570	575
Pro Ile Ala Leu Lys Gly Thr Asp Thr Gly Val Phe Ser Gly Leu Met			
	580	585	590
Gly Gln Gly Tyr Gly Ser Gly Ala Val Ala Pro Glu Leu Glu Gly Phe			
	595	600	605
Val Thr Thr Gly Val Ala Ser Ser Val Ala Ser Gly Arg Val Ser Tyr			
	610	615	620
Val Leu Gly Leu Glu Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser			
625	630	635	640
Ser Ser Leu Val Ala Met His Leu Ala Ala Gln Ala Leu Arg Gln Gly			
	645	650	655
Glu Cys Ser Met Ala Leu Ala Gly Gly Val Thr Val Met Ala Thr Pro			
	660	665	670

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Gly Ser Phe Val Glu Phe Ser Arg Gln Arg Ala Leu Ala Pro Asp Gly
 675 680 685

Arg Cys Lys Ala Phe Ala Ala Ala Ala Asp Gly Thr Gly Trp Ser Glu
 690 695 700

Gly Val Gly Val Val Val Leu Glu Arg Leu Ser Val Ala Arg Glu Arg
 705 710 715 720

Gly His Arg Ile Leu Ala Val Leu Arg Gly Ser Ala Val Asn Gln Asp
 725 730 735

Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Leu Ser Gln Gln Arg
 740 745 750

Val Ile Arg Arg Ala Leu Ala Ala Ala Gly Leu Ala Pro Ser Asp Val
 755 760 765

Asp Val Val Glu Ala His Gly Thr Gly Thr Thr Leu Gly Asp Pro Ile
 770 775 780

Glu Ala Gln Ala Leu Leu Ala Thr Tyr Gly Gln Glu Arg Lys Gln Pro
 785 790 795 800

Leu Trp Leu Gly Ser Leu Lys Ser Asn Ile Gly His Ala Gln Ala Ala
 805 810 815

Ala Gly Val Ala Gly Val Ile Lys Met Val Gln Ala Leu Arg His Glu
 820 825 830

Thr Leu Pro Pro Thr Leu His Val Asp Lys Pro Thr Leu Glu Val Asp
 835 840 845

Trp Ser Ala Gly Ala Ile Glu Leu Leu Thr Glu Ala Arg Ala Trp Pro
 850 855 860

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Arg Asn Gly Arg Pro Arg Arg Ala Gly Val Ser Ser Phe Gly Val Ser
865 870 875 880

Gly Thr Asn Ala His Leu Ile Leu Glu Glu Ala Pro Ala Glu Glu Pro
885 890 895

Val Ala Ala Pro Glu Leu Pro Val Val Pro Leu Val Val Ser Ala Arg
900 905 910

Ser Thr Glu Ser Leu Ser Gly Gln Ala Glu Arg Leu Ala Ser Leu Leu
915 920 925

Glu Gly Asp Val Ser Leu Thr Glu Val Ala Gly Ala Leu Val Ser Arg
930 935 940

Arg Ala Val Leu Asp Glu Arg Ala Val Val Val Ala Gly Ser Arg Glu
945 950 955 960

Glu Ala Val Thr Gly Leu Arg Ala Leu Asn Thr Ala Gly Ser Gly Thr
965 970 975

Pro Gly Lys Val Val Trp Val Phe Pro Gly Gln Gly Thr Gln Trp Ala
980 985 990

Gly Met Gly Arg Glu Leu Leu Ala Glu Ser Pro Val Phe Ala Glu Arg
995 1000 1005

Ile Ala Glu Cys Ala Ala Ala Leu Ala Pro Trp Ile Asp Trp Ser Leu
1010 1015 1020

Val Asp Val Leu Arg Gly Glu Gly Asp Leu Gly Arg Val Asp Val Leu
1025 1030 1035 1040

Gln Pro Ala Cys Phe Ala Val Met Val Gly Leu Ala Ala Val Trp Glu
1045 1050 1055

Ser Val Gly Val Arg Pro Asp Ala Val Val Gly His Ser Gln Gly Glu

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1060	1065	1070
Ile Ala Ala Ala Cys Val Ser Gly Ala Leu Ser Leu Glu Asp Ala Ala		
1075	1080	1085
Lys Val Val Ala Leu Arg Ser Gln Ala Ile Ala Ala Glu Leu Ser Gly		
1090	1095	1100
Arg Gly Gly Met Ala Ser Val Ala Leu Gly Glu Asp Asp Val Val Ser		
1105	1110	1115 1120
Arg Leu Val Asp Gly Val Glu Val Ala Ala Val Asn Gly Pro Ser Ser		
1125	1130	1135
Val Val Ile Ala Gly Asp Ala His Ala Leu Asp Ala Thr Leu Glu Ile		
1140	1145	1150
Leu Ser Gly Glu Gly Ile Arg Val Arg Arg Val Ala Val Asp Tyr Ala		
1155	1160	1165
Ser His Thr Arg His Val Glu Asp Ile Arg Asp Thr Leu Ala Glu Thr		
1170	1175	1180
Leu Ala Gly Ile Ser Ala Gln Ala Pro Ala Val Pro Phe Tyr Ser Thr		
1185	1190	1195 1200
Val Thr Ser Glu Trp Val Arg Asp Ala Gly Val Leu Asp Gly Gly Tyr		
1205	1210	1215
Trp Tyr Arg Asn Leu Arg Asn Gln Val Arg Phe Gly Ala Ala Ala Thr		
1220	1225	1230
Ala Leu Leu Glu Gln Gly His Thr Val Phe Val Glu Val Ser Ala His		
1235	1240	1245
Pro Val Thr Val Gln Pro Leu Ser Glu Leu Thr Gly Asp Ala Ile Gly		
1250	1255	1260

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Thr Leu Arg Arg Glu Asp Gly Gly Leu Arg Arg Leu Leu Ala Ser Met
1265 1270 1275 1280

Gly Glu Leu Phe Val Arg Gly Ile Asp Val Asp Trp Thr Ala Met Val
1285 1290 1295

Pro Ala Ala Gly Trp Val Asp Leu Pro Thr Tyr Ala Phe Glu His Arg
1300 1305 1310

His Tyr Trp Leu Glu Pro Ala Glu Pro Ala Ser Ala Gly Asp Pro Leu
1315 1320 1325

Leu Gly Thr Val Val Ser Thr Pro Gly Ser Asp Arg Leu Thr Ala Val
1330 1335 1340

Ala Gln Trp Ser Arg Arg Ala Gln Pro Trp Ala Val Asp Gly Leu Val
1345 1350 1355 1360

Pro Asn Ala Ala Leu Val Glu Ala Ala Ile Arg Leu Gly Asp Leu Ala
1365 1370 1375

Gly Thr Pro Val Val Gly Glu Leu Val Val Asp Ala Pro Val Val Leu
1380 1385 1390

Pro Arg Arg Gly Ser Arg Glu Val Gln Leu Ile Val Gly Glu Pro Gly
1395 1400 1405

Glu Gln Arg Arg Arg Pro Ile Glu Val Phe Ser Arg Glu Ala Asp Glu
1410 1415 1420

Pro Trp Thr Arg His Ala His Gly Thr Leu Ala Pro Ala Ala Ala Ala
1425 1430 1435 1440

Val Pro Glu Pro Ala Ala Ala Gly Asp Ala Thr Asp Val Thr Val Ala
1445 1450 1455

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Gly Leu Arg Asp Ala Asp Arg Tyr Gly Ile His Pro Ala Leu Leu Asp
1460 1465 1470

Ala Ala Val Arg Thr Val Val Gly Asp Asp Leu Leu Pro Ser Val Trp
1475 1480 1485

Thr Gly Val Ser Leu Leu Ala Ser Gly Ala Thr Ala Val Thr Val Thr
1490 1495 1500

Pro Thr Ala Thr Gly Leu Arg Leu Thr Asp Pro Ala Gly Gln Pro Val
1505 1510 1515 1520

Leu Thr Val Glu Ser Val Arg Gly Thr Pro Phe Val Ala Glu Gln Gly
1525 1530 1535

Thr Thr Asp Ala Leu Phe Arg Val Asp Trp Pro Glu Ile Pro Leu Pro
1540 1545 1550

Thr Ala Glu Thr Ala Asp Phe Leu Pro Tyr Glu Ala Thr Ser Ala Glu
1555 1560 1565

Ala Thr Leu Ser Ala Leu Gln Ala Trp Leu Ala Asp Pro Ala Glu Thr
1570 1575 1580

Arg Leu Ala Val Val Thr Gly Asp Cys Thr Glu Pro Gly Ala Ala Ala
1585 1590 1595 1600

Ile Trp Gly Leu Val Arg Ser Ala Gln Ser Glu His Pro Gly Arg Ile
1605 1610 1615

Val Leu Ala Asp Leu Asp Asp Pro Ala Val Leu Pro Ala Val Val Ala
1620 1625 1630

Ser Gly Glu Pro Gln Val Arg Val Arg Asn Gly Val Ala Ser Val Pro
1635 1640 1645

Arg Leu Thr Arg Val Thr Pro Arg Gln Asp Ala Arg Pro Leu Asp Pro

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1650	1655	1660	
Glu Gly Thr Val Leu Ile Thr Gly Gly Thr Gly Thr Leu Gly Ala Leu			
1665	1670	1675	1680
Thr Ala Arg His Leu Val Thr Ala His Gly Val Arg His Leu Val Leu			
	1685	1690	1695
Val Ser Arg Arg Gly Glu Ala Pro Glu Leu Gln Glu Glu Leu Thr Ala			
	1700	1705	1710
Leu Gly Ala Ser Val Ala Ile Ala Ala Cys Asp Val Ala Asp Arg Ala			
	1715	1720	1725
Gln Leu Glu Ala Val Leu Arg Ala Ile Pro Ala Glu His Pro Leu Thr			
	1730	1735	1740
Ala Val Ile His Thr Ala Gly Val Leu Asp Asp Gly Val Val Thr Glu			
1745	1750	1755	1760
Leu Thr Pro Asp Arg Leu Ala Thr Val Arg Arg Pro Lys Val Asp Ala			
	1765	1770	1775
Ala Arg Leu Leu Asp Glu Leu Thr Arg Glu Ala Asp Leu Ala Ala Phe			
	1780	1785	1790
Val Leu Phe Ser Ser Ala Ala Gly Val Leu Gly Asn Pro Gly Gln Ala			
	1795	1800	1805
Gly Tyr Ala Ala Ala Asn Ala Glu Leu Asp Ala Leu Ala Arg Gln Arg			
	1810	1815	1820
Asn Ser Leu Asp Leu Pro Ala Val Ser Ile Ala Trp Gly Tyr Trp Ala			
1825	1830	1835	1840
Thr Val Ser Gly Met Thr Glu His Leu Gly Asp Ala Asp Leu Arg Arg			
	1845	1850	1855

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Asn Gln Arg Ile Gly Met Ser Gly Leu Pro Ala Asp Glu Gly Met Ala
 1860 1865 1870

Leu Leu Asp Ala Ala Ile Ala Thr Gly Gly Thr Leu Val Ala Ala Lys
 1875 1880 1885

Phe Asp Val Ala Ala Leu Arg Ala Thr Ala Lys Ala Gly Gly Pro Val
 1890 1895 1900

Pro Pro Leu Leu Arg Gly Leu Ala Pro Leu Pro Arg Arg Ala Ala Ala
 1905 1910 1915 1920

Lys Thr Ala Ser Leu Thr Glu Arg Leu Ala Gly Leu Ala Glu Thr Glu
 1925 1930 1935

Gln Ala Ala Ala Leu Leu Asp Leu Val Arg Arg His Ala Ala Glu Val
 1940 1945 1950

Leu Gly His Ser Gly Ala Glu Ser Val His Ser Gly Arg Thr Phe Lys
 1955 1960 1965

Asp Ala Gly Phe Asp Ser Leu Thr Ala Val Glu Leu Arg Asn Arg Leu
 1970 1975 1980

Ala Ala Ala Thr Gly Leu Thr Leu Ser Pro Ala Met Ile Phe Asp Tyr
 1985 1990 1995 2000

Pro Lys Pro Pro Ala Leu Ala Asp His Leu Arg Ala Lys Leu Phe Gly
 2005 2010 2015

Ser Ala Ala Asn Arg Pro Ala Glu Ile Gly Thr Ala Ala Ala Glu Glu
 2020 2025 2030

Pro Ile Ala Ile Val Ala Met Ala Cys Arg Phe Pro Gly Gly Val His
 2035 2040 2045

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Ser Pro Glu Asp Leu Trp Arg Leu Val Ala Asp Gly Ala Asp Ala Val
 2050 2055 2060

Thr Glu Phe Pro Ala Asp Arg Gly Trp Asp Thr Asp Arg Leu Tyr His
 2065 2070 2075 2080

Glu Asp Pro Asp His Glu Gly Thr Thr Tyr Val Arg His Gly Ala Phe
 2085 2090 2095

Leu Asp Asp Ala Ala Gly Phe Asp Ala Ala Phe Phe Gly Ile Ser Pro
 2100 2105 2110

Asn Glu Ala Leu Ala Met Asp Pro Gln Gln Arg Leu Leu Leu Glu Thr
 2115 2120 2125

Ser Trp Glu Leu Phe Glu Arg Ala Ala Ile Asp Pro Thr Thr Leu Ala
 2130 2135 2140

Gly Gln Asp Ile Gly Val Phe Ala Gly Val Asn Ser His Asp Tyr Ser
 2145 2150 2155 2160

Met Arg Met His Arg Ala Ala Gly Val Glu Gly Phe Arg Leu Thr Gly
 2165 2170 2175

Gly Ser Ala Ser Val Leu Ser Gly Arg Val Ala Tyr His Phe Gly Val
 2180 2185 2190

Glu Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser Ser Leu Val
 2195 2200 2205

Ala Leu His Met Ala Val Gln Ala Leu Gln Arg Gly Glu Cys Ser Met
 2210 2215 2220

Ala Leu Ala Gly Gly Val Met Val Met Gly Thr Val Glu Thr Phe Val
 2225 2230 2235 2240

Glu Phe Ser Arg Gln Arg Gly Leu Ala Pro Asp Gly Arg Cys Lys Ala

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2245	2250	2255
Phe Ala Asp Gly Ala Asp Gly Thr Gly Trp Ser Glu Gly Val Gly Leu		
2260	2265	2270
Leu Leu Val Glu Arg Leu Ser Glu Ala Gln Arg Arg Gly His Gln Val		
2275	2280	2285
Leu Ala Val Val Arg Gly Ser Ala Val Asn Ser Asp Gly Ala Ser Asn		
2290	2295	2300
Gly Leu Thr Ala Pro Asn Gly Pro Ser Gln Gln Arg Val Ile Arg Lys		
2305	2310	2315 2320
Ala Leu Ala Ala Ala Gly Leu Ser Thr Ser Asp Val Asp Ala Val Glu		
2325	2330	2335
Ala His Gly Thr Gly Thr Thr Leu Gly Asp Pro Ile Glu Ala Glu Ala		
2340	2345	2350
Leu Leu Ala Thr Tyr Gly Gln Asn Arg Glu Thr Pro Leu Trp Leu Gly		
2355	2360	2365
Ser Val Lys Ser Asn Leu Gly His Thr Gln Ala Ala Ala Gly Val Ala		
2370	2375	2380
Gly Val Ile Lys Met Val Met Ala Met Arg His Gly Val Leu Pro Arg		
2385	2390	2395 2400
Thr Leu His Val Asp Arg Pro Ser Ser Tyr Val Asp Trp Ser Ala Gly		
2405	2410	2415
Ala Val Glu Leu Leu Thr Glu Ala Arg Asp Trp Val Ser Asn Gly His		
2420	2425	2430
Pro Arg Arg Ala Gly Val Ser Ser Phe Gly Ile Gly Gly Thr Asn Ala		
2435	2440	2445

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His Val Val Leu Glu Glu Val Ala Ala Pro Ile Thr Thr Pro Gln Pro
2450 2455 2460

Glu Pro Ala Glu Phe Leu Val Pro Val Leu Val Ser Ala Arg Thr Ala
2465 2470 2475 2480

Ala Gly Leu Arg Gly Gln Ala Gly Arg Leu Ala Ala Phe Leu Gly Asp
2485 2490 2495

Arg Thr Asp Val Arg Val Pro Asp Ala Ala Tyr Ala Leu Ala Thr Thr
2500 2505 2510

Arg Ala Gln Leu Asp His Arg Ala Val Val Leu Ala Ser Asp Arg Ala
2515 2520 2525

Gln Leu Cys Ala Asp Leu Ala Ala Phe Gly Ser Gly Val Val Thr Gly
2530 2535 2540

Thr Pro Val Asp Gly Lys Leu Ala Val Leu Phe Thr Gly Gln Gly Ser
2545 2550 2555 2560

Gln Trp Ala Gly Met Gly Arg Glu Leu Ala Glu Thr Phe Pro Val Phe
2565 2570 2575

Arg Asp Ala Phe Glu Ala Ala Cys Glu Ala Val Asp Thr His Leu Arg
2580 2585 2590

Glu Arg Pro Leu Arg Glu Val Val Phe Asp Asp Ser Ala Leu Leu Asp
2595 2600 2605

Gln Thr Met Tyr Thr Gln Gly Ala Leu Phe Ala Val Glu Thr Ala Leu
2610 2615 2620

Phe Arg Leu Phe Glu Ser Trp Gly Val Arg Pro Gly Leu Leu Ala Gly
2625 2630 2635 2640

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His Ser Ile Gly Glu Leu Ala Ala Ala His Val Ser Gly Val Leu Asp
2645 2650 2655

Leu Ala Asp Ala Gly Glu Leu Val Ala Ala Arg Gly Arg Leu Met Gln
2660 2665 2670

Ala Leu Pro Ala Gly Gly Ala Met Val Ala Val Gln Ala Thr Glu Asp
2675 2680 2685

Glu Val Ala Pro Leu Leu Asp Gly Thr Val Cys Val Ala Ala Val Asn
2690 2695 2700

Gly Pro Asp Ser Val Val Leu Ser Gly Thr Glu Ala Ala Val Leu Ala
2705 2710 2715 2720

Val Ala Asp Glu Leu Ala Gly Arg Gly Arg Lys Thr Arg Arg Leu Ala
2725 2730 2735

Val Ser His Ala Phe His Ser Pro Leu Met Glu Pro Met Leu Asp Asp
2740 2745 2750

Phe Arg Ala Val Ala Glu Arg Leu Thr Tyr Arg Ala Gly Ser Leu Pro
2755 2760 2765

Val Val Ser Thr Leu Thr Gly Glu Leu Ala Ala Leu Asp Ser Pro Asp
2770 2775 2780

Tyr Trp Val Gly Gln Val Arg Asn Ala Val Arg Phe Ser Asp Ala Val
2785 2790 2795 2800

Thr Ala Leu Gly Ala Gln Gly Ala Ser Thr Phe Leu Glu Leu Gly Pro
2805 2810 2815

Gly Gly Ala Leu Ala Ala Met Ala Leu Gly Thr Leu Gly Gly Pro Glu
2820 2825 2830

Gln Ser Cys Val Ala Thr Leu Arg Lys Asn Gly Ala Glu Val Pro Asp

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2835	2840	2845
Val Leu Thr Ala Leu Ala Glu Leu His Val Arg Gly Val Gly Val Asp		
2850	2855	2860
Trp Thr Thr Val Leu Asp Glu Pro Ala Thr Ala Val Gly Thr Val Leu		
2865	2870	2875 2880
Pro Thr Tyr Ala Phe Gln His Gln Arg Phe Trp Val Asp Val Asp Glu		
2885	2890	2895
Thr Ala Ala Val Ser Val Thr Pro Pro Pro Ala Glu Pro Ile Val Asp		
2900	2905	2910
Arg Pro Val Gln Asp Val Leu Glu Leu Val Arg Glu Ser Ala Ala Val		
2915	2920	2925
Val Leu Gly His Arg Asp Ala Gly Ser Phe Asp Leu Asp Arg Ser Phe		
2930	2935	2940
Lys Asp His Gly Phe Asp Ser Leu Ser Ala Val Lys Leu Arg Asn Arg		
2945	2950	2955 2960
Leu Arg Asp Phe Thr Gly Val Glu Leu Pro Ser Thr Leu Ile Phe Asp		
2965	2970	2975
Tyr Pro Asn Pro Ala Val Leu Ala Asp His Leu Arg Ala Glu Leu Leu		
2980	2985	2990
Gly Glu Arg Pro Ala Ala Pro Ala Pro Val Thr Arg Asp Val Ser Asp		
2995	3000	3005
Glu Pro Ile Ala Ile Val Gly Met Ser Thr Arg Leu Pro Gly Gly Ala		
3010	3015	3020
Asp Ser Pro Glu Glu Leu Trp Lys Leu Val Ala Glu Gly Arg Asp Ala		
3025	3030	3035 3040

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Val Ser Gly Phe Pro Val Asp Arg Gly Trp Asp Leu Asp Gly Leu Tyr
3045 3050 3055

His Pro Asp Pro Ala His Ala Gly Thr Ser Tyr Thr Arg Ser Gly Gly
3060 3065 3070

Phe Leu His Asp Ala Ala Gln Phe Asp Ala Gly Leu Phe Gly Ile Ser
3075 3080 3085

Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg Leu Leu Leu Glu
3090 3095 3100

Thr Ser Trp Glu Ala Leu Glu Arg Ala Gly Val Asp Pro Leu Ser Ala
3105 3110 3115 3120

Arg Gly Ser Asp Val Gly Val Phe Thr Gly Ile Val His His Asp Tyr
3125 3130 3135

Val Thr Arg Leu Arg Glu Val Pro Glu Asp Val Gln Gly Tyr Thr Met
3140 3145 3150

Thr Gly Thr Ala Ser Ser Val Ala Ser Gly Arg Val Ala Tyr Val Phe
3155 3160 3165

Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser Ser
3170 3175 3180

Leu Val Ala Met His Leu Ala Ala Gln Ala Leu Arg Gln Gly Glu Cys
3185 3190 3195 3200

Ser Met Ala Leu Ala Gly Gly Ala Thr Val Met Ala Ser Pro Asp Ala
3205 3210 3215

Phe Leu Glu Phe Ser Arg Gln Arg Gly Leu Ser Ala Asp Gly Arg Cys
3220 3225 3230

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Lys Ala Tyr Ala Glu Gly Ala Asp Gly Thr Gly Trp Ala Glu Gly Val
3235 3240 3245

Gly Val Val Val Leu Glu Arg Leu Ser Val Ala Arg Glu Arg Gly His
3250 3255 3260

Arg Val Leu Ala Val Leu Arg Gly Ser Ala Val Asn Gln Asp Gly Ala
3265 3270 3275 3280

Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser Gln Gln Arg Val Ile
3285 3290 3295

Arg Gly Ala Leu Ala Ser Ala Gly Leu Ala Pro Ser Asp Val Asp Val
3300 3305 3310

Val Glu Gly His Gly Thr Gly Thr Ala Leu Gly Asp Pro Ile Glu Val
3315 3320 3325

Gln Ala Leu Leu Ala Thr Tyr Gly Gln Glu Arg Glu Gln Pro Leu Trp
3330 3335 3340

Leu Gly Ser Leu Lys Ser Asn Leu Gly His Thr Gln Ala Ala Ala Gly
3345 3350 3355 3360

Val Val Gly Val Ile Lys Met Ile Met Ala Met Arg His Gly Val Met
3365 3370 3375

Pro Ala Thr Leu His Val Asp Glu Arg Thr Ser Gln Val Asp Trp Ser
3380 3385 3390

Ala Gly Ala Ile Glu Val Leu Thr Glu Ala Arg Glu Trp Pro Arg Thr
3395 3400 3405

Gly Arg Pro Arg Arg Ala Gly Val Ser Ser Phe Gly Ala Ser Gly Thr
3410 3415 3420

Asn Ala His Leu Ile Ile Glu Glu Gly Pro Ala Glu Glu Ala Val Asp

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3425	3430	3435	3440
Glu Glu Val Ala Ser Val Val Pro Leu Val Val Ser Ala Arg Ser Ala			
3445	3450	3455	
Gly Ser Leu Ala Gly Gln Ala Gly Arg Leu Ala Ala Val Leu Glu Asn			
3460	3465	3470	
Glu Ser Leu Ala Gly Val Ala Gly Ala Leu Val Ser Gly Arg Ala Thr			
3475	3480	3485	
Leu Asn Glu Arg Ala Val Val Ile Ala Gly Ser Arg Asp Glu Ala Gln			
3490	3495	3500	
Asp Gly Leu Gln Ala Leu Ala Arg Gly Glu Asn Ala Pro Gly Val Val			
3505	3510	3515	3520
Thr Gly Thr Ala Gly Lys Pro Gly Lys Val Val Trp Val Phe Pro Gly			
3525	3530	3535	
Gln Gly Ser Gln Trp Met Gly Met Gly Arg Asp Leu Leu Asp Ser Ser			
3540	3545	3550	
Pro Val Phe Ala Ala Arg Ile Lys Glu Cys Ala Ala Ala Leu Glu Gln			
3555	3560	3565	
Trp Thr Asp Trp Ser Leu Leu Asp Val Leu Arg Gly Asp Ala Asp Leu			
3570	3575	3580	
Leu Asp Arg Val Asp Val Val Gln Pro Ala Ser Phe Ala Met Met Val			
3585	3590	3595	3600
Gly Leu Ala Ala Val Trp Thr Ser Leu Gly Val Thr Pro Asp Ala Val			
3605	3610	3615	
Leu Gly His Ser Gln Gly Glu Ile Ala Ala Ala Cys Val Ser Gly Ala			
3620	3625	3630	

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Leu Ser Leu Asp Asp Ala Ala Lys Val Val Ala Leu Arg Ser Gln Ala
3635 3640 3645

Ile Ala Gly Glu Leu Ala Gly Arg Gly Gly Met Ala Ser Val Ala Leu
3650 3655 3660

Ser Glu Glu Asp Ala Val Ala Arg Leu Thr Pro Trp Ala Asn Arg Val
3665 3670 3675 3680

Glu Val Ala Ala Val Asn Ser Pro Ser Ser Val Val Ile Ala Gly Asp
3685 3690 3695

Ala Gln Ala Leu Asp Glu Ala Leu Glu Ala Leu Ala Gly Asp Gly Val
3700 3705 3710

Arg Val Arg Arg Val Ala Val Asp Tyr Ala Ser His Thr Arg His Val
3715 3720 3725

Glu Ala Ile Ala Glu Thr Leu Ala Lys Thr Leu Ala Gly Ile Asp Ala
3730 3735 3740

Arg Val Pro Ala Ile Pro Phe Tyr Ser Thr Val Leu Gly Thr Trp Ile
3745 3750 3755 3760

Glu Gln Ala Val Val Asp Ala Gly Tyr Trp Tyr Arg Asn Leu Arg Gln
3765 3770 3775

Gln Val Arg Phe Gly Pro Ser Val Ala Asp Leu Ala Gly Leu Gly His
3780 3785 3790

Thr Val Phe Val Glu Ile Ser Ala His Pro Val Leu Val Gln Pro Leu
3795 3800 3805

Ser Glu Ile Ser Asp Asp Ala Val Val Thr Gly Ser Leu Arg Arg Asp
3810 3815 3820

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Asp Gly Gly Leu Arg Arg Leu Leu Ala Ser Ala Ala Glu Leu Tyr Val
3825 3830 3835 3840

Arg Gly Val Ala Val Asp Trp Thr Ala Ala Val Pro Ala Ala Gly Trp
3845 3850 3855

Val Asp Leu Pro Thr Tyr Ala Phe Asp Arg Arg His Phe Trp Leu His
3860 3865 3870

Glu Ala Glu Thr Ala Glu Ala Ala Glu Gly Met Asp Gly Glu Phe Trp
3875 3880 3885

Thr Ala Ile Glu Gln Ser Asp Val Asp Ser Leu Ala Glu Leu Leu Glu
3890 3895 3900

Leu Val Pro Glu Gln Arg Gly Ala Leu Ser Thr Val Val Pro Val Leu
3905 3910 3915 3920

Ala Gln Trp Arg Asp Arg Arg Arg Glu Arg Ser Thr Ala Glu Lys Leu
3925 3930 3935

Arg Tyr Gln Val Thr Trp Gln Pro Leu Glu Arg Glu Ala Ala Gly Val
3940 3945 3950

Pro Gly Gly Arg Trp Leu Ala Val Val Pro Ala Gly Thr Thr Asp Ala
3955 3960 3965

Leu Leu Lys Glu Leu Thr Gly Gln Gly Leu Asp Ile Val Arg Leu Glu
3970 3975 3980

Ile Glu Glu Ala Ser Arg Ala Gln Leu Ala Glu Gln Leu Arg Asn Val
3985 3990 3995 4000

Leu Ala Glu His Asp Leu Thr Gly Val Leu Ser Leu Leu Ala Leu Asp
4005 4010 4015

Gly Gly Pro Ala Asp Ala Ala Glu Ile Thr Ala Ser Thr Leu Ala Leu

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4020	4025	4030
Val Gln Ala Leu Gly Asp Thr Thr Thr Ser Ala Pro Leu Trp Cys Leu		
4035	4040	4045
Thr Ser Gly Ala Val Asn Ile Gly Ile Gln Asp Ala Val Thr Ala Pro		
4050	4055	4060
Ala Gln Ala Ala Val Trp Gly Leu Gly Arg Ala Val Ala Leu Glu Arg		
4065	4070	4075 4080
Leu Asp Arg Trp Gly Gly Leu Val Asp Leu Pro Ala Ala Ile Asp Ala		
4085	4090	4095
Arg Thr Ala Gln Ala Leu Leu Gly Val Leu Asn Gly Ala Ala Gly Glu		
4100	4105	4110
Asp Gln Leu Ala Val Arg Arg Ser Gly Val Tyr Arg Arg Arg Leu Val		
4115	4120	4125
Arg Lys Pro Val Pro Glu Ser Ala Thr Ser Arg Trp Glu Pro Arg Gly		
4130	4135	4140
Thr Val Leu Val Thr Gly Gly Ala Glu Gly Leu Gly Arg His Ala Ser		
4145	4150	4155 4160
Val Trp Leu Ala Gln Ser Gly Ala Glu Arg Leu Ile Val Thr Gly Thr		
4165	4170	4175
Asp Gly Val Asp Glu Leu Thr Ala Glu Leu Ala Glu Phe Gly Thr Thr		
4180	4185	4190
Val Glu Phe Cys Ala Asp Thr Asp Arg Asp Ala Ile Ala Gln Leu Val		
4195	4200	4205
Ala Asp Ser Glu Val Thr Ala Val Val His Ala Ala Asp Ile Ala Gln		
4210	4215	4220

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Thr Ser Ser Val Asp Asp Thr Gly Val Ala Asp Leu Asp Glu Val Phe
 4225 4230 4235 4240

Ala Ala Lys Val Thr Thr Ala Val Trp Leu Asp Gln Leu Phe Glu Asp
 4245 4250 4255

Thr Pro Leu Asp Ala Phe Val Val Phe Ser Ser Ile Ala Gly Ile Trp
 4260 4265 4270

Gly Gly Gly Gly Gln Gly Pro Ala Gly Ala Ala Asn Ala Val Leu Asp
 4275 4280 4285

Ala Leu Val Glu Trp Arg Arg Ala Arg Gly Leu Lys Ala Thr Ser Ile
 4290 4295 4300

Ala Trp Gly Ala Leu Asp Gln Ile Gly Ile Gly Met Asp Glu Ala Ala
 4305 4310 4315 4320

Leu Ala Gln Leu Arg Arg Arg Gly Val Ile Pro Met Ala Pro Pro Leu
 4325 4330 4335

Ala Val Thr Ala Met Val Gln Ala Val Ala Gly Asn Glu Lys Ala Val
 4340 4345 4350

Ala Val Ala Asp Met Asp Trp Ala Ala Phe Ile Pro Ala Phe Thr Ser
 4355 4360 4365

Val Arg Pro Ser Pro Leu Phe Ala Asp Leu Pro Glu Ala Lys Ala Ile
 4370 4375 4380

Leu Arg Ala Ala Gln Asp Asp Gly Glu Asp Gly Asp Thr Ala Ser Ser
 4385 4390 4395 4400

Leu Ala Asp Ser Leu Arg Ala Val Pro Asp Ala Glu Gln Asn Arg Ile
 4405 4410 4415

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Leu Leu Lys Leu Val Arg Gly His Ala Ser Thr Val Leu Gly His Ser
4420 4425 4430

Gly Ala Glu Gly Ile Gly Pro Arg Gln Ala Phe Gln Glu Val Gly Phe
4435 4440 4445

Asp Ser Leu Ala Ala Val Asn Leu Arg Asn Ser Leu His Ala Ala Thr
4450 4455 4460

Gly Leu Arg Leu Pro Ala Thr Leu Ile Phe Asp Tyr Pro Thr Pro Glu
4465 4470 4475 4480

Ala Leu Val Gly Tyr Leu Arg Val Glu Leu Leu Arg Glu Ala Asp Asp
4485 4490 4495

Gly Leu Asp Gly Arg Glu Asp Asp Leu Arg Arg Val Leu Ala Ala Val
4500 4505 4510

Pro Phe Ala Arg Phe Lys Glu Ala Gly Val Leu Asp Thr Leu Leu Gly
4515 4520 4525

Leu Ala Asp Thr Gly Thr Glu Pro Gly Thr Asp Ala Glu Thr Thr Glu
4530 4535 4540

Ala Ala Pro Ala Ala Asp Asp Ala Glu Leu Ile Asp Ala Leu Asp Ile
4545 4550 4555 4560

Ser Gly Leu Val Gln Arg Ala Leu Gly Gln Thr Ser
4565 4570

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5069 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Met	Ala	Asn	Gln	Ser	Trp	Arg	Lys	Asn	Met	Ser	Ala	Pro	Asn	Glu	Gln
1				5					10					15	
Ile	Val	Asp	Ala	Leu	Arg	Ala	Ser	Leu	Lys	Glu	Asn	Val	Arg	Leu	Gln
			20					25					30		
Gln	Glu	Asn	Ser	Ala	Leu	Ala	Ala	Ala	Ala	Glu	Pro	Val	Ala	Ile	
		35					40				45				
Val	Ser	Met	Ala	Cys	Arg	Tyr	Ala	Gly	Gly	Ile	Arg	Gly	Pro	Glu	Asp
	50					55					60				
Phe	Trp	Arg	Val	Val	Ser	Glu	Gly	Ala	Asp	Val	Tyr	Thr	Gly	Phe	Pro
65					70					75					80
Glu	Asp	Arg	Gly	Trp	Asp	Val	Glu	Gly	Leu	Tyr	His	Pro	Asp	Pro	Asp
			85						90				95		
Asn	Pro	Gly	Thr	Thr	Tyr	Val	Arg	Glu	Gly	Ala	Phe	Leu	Gln	Asp	Ala
			100						105				110		
Ala	Gln	Phe	Asp	Ala	Gly	Phe	Phe	Gly	Ile	Ser	Pro	Arg	Glu	Ala	Leu
		115						120					125		
Ala	Met	Asp	Pro	Gln	Gln	Arg	Gln	Leu	Leu	Glu	Val	Ser	Trp	Glu	Thr
	130						135						140		
Leu	Glu	Arg	Ala	Gly	Ile	Asp	Pro	His	Ser	Val	Arg	Gly	Ser	Asp	Ile
145						150						155			160

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Gly Val Tyr Ala Gly Val Val His Gln Asp Tyr Ala Pro Asp Leu Ser
165 170 175

Gly Phe Glu Gly Phe Met Ser Leu Glu Arg Ala Leu Gly Thr Ala Gly
180 185 190

Gly Val Ala Ser Gly Arg Val Ala Tyr Thr Leu Gly Leu Glu Gly Pro
195 200 205

Ala Val Thr Val Asp Thr Met Cys Ser Ser Ser Leu Val Ala Ile His
210 215 220

Leu Ala Ala Gln Ala Leu Arg Arg Gly Glu Cys Ser Met Ala Leu Ala
225 230 235 240

Gly Gly Ser Thr Val Met Ala Thr Pro Gly Gly Phe Val Gly Phe Ala
245 250 255

Arg Gln Arg Ala Leu Ala Phe Asp Gly Arg Cys Lys Ser Tyr Ala Ala
260 265 270

Ala Ala Asp Gly Ser Gly Trp Ala Glu Gly Val Gly Val Leu Leu Leu
275 280 285

Glu Arg Leu Ser Val Ala Arg Glu Arg Gly His Gln Val Leu Ala Val
290 295 300

Ile Arg Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr
305 310 315 320

Ala Pro Asn Gly Pro Ala Gln Gln Arg Val Ile Arg Lys Ala Leu Ala
325 330 335

Ser Ala Gly Leu Thr Pro Ser Asp Val Asp Thr Val Glu Gly His Gly
340 345 350

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Thr Gly Thr Val Leu Gly Asp Pro Ile Glu Val Gln Ala Leu Leu Ala
 355 360 365

Thr Tyr Gly Gln Gly Arg Asp Pro Gln Gln Pro Leu Trp Leu Gly Ser
 370 375 380

Val Lys Ser Val Val Gly His Thr Gln Ala Ala Ser Gly Val Ala Gly
 385 390 395 400

Val Ile Lys Met Val Gln Ser Leu Arg His Gly Gln Leu Pro Ala Thr
 405 410 415

Gln His Val Asp Ala Pro Thr Pro Gln Val Asp Trp Ser Ala Gly Ala
 420 425 430

Ile Glu Leu Leu Ala Glu Gly Arg Glu Trp Pro Arg Asn Gly His Pro
 435 440 445

Arg Arg Gly Gly Ile Ser Ser Phe Gly Ala Ser Gly Thr Asn Ala His
 450 455 460

Met Ile Leu Glu Glu Ala Pro Glu Asp Glu Pro Val Thr Glu Ala Pro
 465 470 475 480

Ala Pro Thr Gly Val Val Pro Leu Val Val Ser Ala Ala Thr Ala Ala
 485 490 495

Ser Leu Ala Ala Gln Ala Gly Arg Leu Ala Glu Val Gly Asp Val Ser
 500 505 510

Leu Ala Asp Val Ala Gly Thr Leu Val Ser Gly Arg Ala Met Leu Ser
 515 520 525

Glu Arg Ala Val Val Val Ala Gly Ser His Glu Glu Ala Val Thr Gly
 530 535 540

Leu Arg Ala Leu Ala Arg Gly Glu Ser Ala Pro Gly Leu Leu Ser Gly

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545	550	555	560
Arg Gly Ser Gly Val Pro Gly Lys Val Val Trp Val Phe Pro Gly Gln			
565	570	575	
Gly Thr Gln Trp Ala Gly Met Gly Arg Glu Leu Leu Asp Ser Ser Glu			
580	585	590	
Val Phe Ala Ala Arg Ile Ala Glu Cys Glu Thr Ala Leu Gly Arg Trp			
595	600	605	
Val Asp Trp Ser Leu Thr Asp Val Leu Arg Gly Glu Ala Asp Leu Leu			
610	615	620	
Asp Arg Val Asp Val Val Gln Pro Ala Ser Phe Ala Val Met Val Gly			
625	630	635	640
Leu Ala Ala Val Trp Ala Ser Leu Gly Val Glu Pro Glu Ala Val Val			
645	650	655	
Gly His Ser Gln Gly Glu Ile Ala Ala Ala Cys Val Ser Gly Ala Leu			
660	665	670	
Ser Leu Glu Asp Ala Ala Lys Val Val Ala Leu Arg Ser Gln Ala Ile			
675	680	685	
Ala Ala Ser Leu Ala Gly Arg Gly Gly Met Ala Ser Val Ala Leu Ser			
690	695	700	
Glu Glu Asp Ala Thr Ala Arg Leu Glu Pro Trp Ala Gly Arg Val Glu			
705	710	715	720
Val Ala Ala Val Asn Gly Pro Thr Ser Val Val Ile Ala Gly Asp Ala			
725	730	735	
Glu Ala Leu Asp Glu Ala Leu Asp Ala Leu Asp Asp Gln Gly Val Arg			
740	745	750	

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Ile Arg Arg Val Ala Val Asp Tyr Ala Ser His Thr Arg His Val Glu
755 760 765

Ala Ala Arg Asp Ala Leu Ala Glu Met Leu Gly Gly Ile Arg Ala Gln
770 775 780

Ala Pro Glu Val Pro Phe Tyr Ser Thr Val Thr Gly Gly Trp Val Glu
785 790 795 800

Asp Ala Gly Val Leu Asp Gly Gly Tyr Trp Tyr Arg Asn Leu Arg Arg
805 810 815

Gln Val Arg Phe Gly Pro Ala Val Ala Glu Leu Ile Glu Gln Gly His
820 825 830

Arg Val Phe Val Glu Val Ser Ala His Pro Val Leu Val Gln Pro Ile
835 840 845

Asn Glu Leu Val Asp Asp Thr Glu Ala Val Val Thr Gly Thr Leu Arg
850 855 860

Arg Glu Asp Gly Gly Leu Arg Arg Leu Leu Ala Ser Ala Ala Glu Leu
865 870 875 880

Phe Val Arg Gly Val Thr Val Asp Trp Ser Gly Val Leu Pro Pro Ser
885 890 895

Arg Arg Val Glu Leu Pro Thr Tyr Ala Phe Asp His Gln His Tyr Trp
900 905 910

Leu Gln Met Gly Gly Ser Ala Thr Asp Ala Val Ser Leu Gly Leu Ala
915 920 925

Gly Ala Asp His Pro Leu Leu Gly Ala Val Val Pro Leu Pro Gln Ser
930 935 940

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Asp Gly Leu Val Phe Thr Ser Arg Leu Ser Leu Lys Ser His Pro Trp
 945 950 955 960

Leu Ala Gly His Ala Ile Gly Gly Val Val Leu Ile Pro Gly Thr Val
 965 970 975

Tyr Val Asp Leu Ala Leu Arg Ala Gly Asp Glu Leu Gly Phe Gly Val
 980 985 990

Leu Glu Glu Leu Val Ile Glu Ala Pro Leu Val Leu Gly Glu Arg Gly
 995 1000 1005

Gly Val Arg Val Gln Val Ala Val Ser Gly Pro Asn Glu Thr Gly Ser
 1010 1015 1020

Arg Ala Val Asp Val Phe Ser Met Arg Glu Asp Gly Asp Glu Trp Thr
 1025 1030 1035 1040

Arg His Ala Thr Gly Leu Leu Gly Ala Ser Thr Ser Arg Glu Pro Ser
 1045 1050 1055

Arg Phe Asp Phe Ala Ala Trp Pro Pro Ala Gly Ala Glu Pro Ile Asp
 1060 1065 1070

Val Glu Asn Phe Tyr Thr Asp Leu Thr Glu Arg Gly Tyr Ala Tyr Ser
 1075 1080 1085

Gly Ala Phe Gln Gly Met Arg Ala Val Trp Arg Arg Gly Asp Glu Val
 1090 1095 1100

Phe Ala Glu Val Ala Leu Pro Asp Asp His Arg Glu Asp Ala Gly Lys
 1105 1110 1115 1120

Phe Gly Leu His Pro Ala Leu Leu Asp Ala Ala Leu His Thr Asn Ala
 1125 1130 1135

Phe Ala Asn Pro Asp Asp Asp Arg Ser Val Leu Pro Phe Ala Trp Asn

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1140	1145	1150
Gly Leu Val Leu His Ala Val Gly Ala Ser Ala Leu Arg Val Arg Val		
1155	1160	1165
Ala Pro Gly Gly Pro Asp Ala Leu Thr Phe Gln Ala Ala Asp Glu Thr		
1170	1175	1180
Gly Gly Leu Val Val Thr Met Asp Ser Leu Val Ser Arg Glu Val Ser		
1185	1190	1195
		1200
Ala Ala Gln Leu Glu Thr Ala Ala Gly Glu Glu Arg Asp Ser Leu Phe		
1205	1210	1215
Gln Val Asp Trp Ile Glu Val Pro Ala Thr Glu Thr Ala Ala Thr Glu		
1220	1225	1230
His Ala Glu Val Leu Glu Ala Phe Gly Glu Ala Ala Pro Leu Glu Leu		
1235	1240	1245
Thr Ser Arg Val Leu Glu Ala Val Gln Ser Trp Leu Ala Asp Ala Ala		
1250	1255	1260
Asp Glu Ala Arg Leu Val Val Val Thr Arg Gly Ala Val Arg Glu Val		
1265	1270	1275
		1280
Thr Asp Pro Ala Gly Ala Ala Val Trp Gly Leu Val Arg Ala Ala Gln		
1285	1290	1295
Ala Glu Asn Pro Gly Arg Ile Ile Leu Val Asp Thr Asp Gly Asp Val		
1300	1305	1310
Pro Leu Gly Ala Val Leu Ala Ser Gly Glu Pro Gln Leu Ala Val Arg		
1315	1320	1325
Gly Asn Ala Phe Ser Val Pro Arg Leu Ala Arg Ala Thr Gly Glu Val		
1330	1335	1340

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Pro Glu Ala Pro Ala Val Phe Ser Pro Glu Gly Thr Val Leu Leu Thr
1345 1350 1355 1360

Gly Gly Thr Gly Ser Leu Gly Gly Leu Val Ala Lys His Leu Val Ala
1365 1370 1375

Arg His Gly Val Arg Arg Leu Val Leu Ala Ser Arg Arg Gly Val Ala
1380 1385 1390

Ala Glu Asp Leu Val Thr Glu Leu Thr Glu Gln Gly Ala Thr Val Ser
1395 1400 1405

Val Val Ala Cys Asp Val Ser Asp Arg Asp Gln Val Ala Ala Leu Leu
1410 1415 1420

Ala Glu His Arg Pro Thr Gly Ile Val His Leu Ala Gly Leu Leu Asp
1425 1430 1435 1440

Asp Gly Val Ile Gly Ala Leu Asn Arg Glu Arg Leu Ala Gly Val Phe
1445 1450 1455

Ala Pro Lys Val Asp Ala Val Gln His Leu Asp Glu Leu Thr Arg Asp
1460 1465 1470

Leu Gly Leu Asp Ala Phe Val Val Phe Ser Ser Ala Ala Ala Leu Met
1475 1480 1485

Gly Ser Ala Gly Gln Gly Asn Tyr Ala Ala Ala Asn Ala Phe Leu Asp
1490 1495 1500

Gly Leu Met Ala Gly Arg Arg Ala Ala Gly Leu Pro Gly Val Ser Leu
1505 1510 1515 1520

Ala Trp Gly Leu Trp Glu Gln Ala Asp Gly Leu Thr Ala Asn Leu Ser
1525 1530 1535

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Ala Thr Asp Gln Ala Arg Met Ser Arg Gly Gly Val Leu Pro Met Thr
1540 1545 1550

Pro Ala Glu Ala Leu Asp Ile Phe Asp Ile Gly Leu Ala Ala Glu Gln
1555 1560 1565

Ala Leu Leu Val Pro Ile Lys Leu Asp Leu Arg Thr Leu Arg Gly Gln
1570 1575 1580

Ala Thr Ala Gly Gly Glu Val Pro His Leu Leu Arg Gly Leu Val Arg
1585 1590 1595 1600

Ala Ser Arg Arg Val Thr Arg Thr Ala Ala Ala Ser Gly Gly Gly Gly
1605 1610 1615

Leu Val His Lys Leu Ala Gly Arg Pro Ala Glu Glu Gln Glu Ala Val
1620 1625 1630

Leu Leu Gly Ile Val Gln Ala Glu Ala Ala Ala Val Leu Gly Phe Asn
1635 1640 1645

Ala Pro Glu Leu Ala Gln Gly Thr Arg Gly Phe Ser Asp Leu Gly Phe
1650 1655 1660

Asp Ser Leu Thr Ala Val Glu Leu Arg Asn Arg Leu Ser Ala Ala Thr
1665 1670 1675 1680

Gly Val Lys Leu Pro Ala Thr Leu Val Phe Asp Tyr Pro Thr Pro Val
1685 1690 1695

Ala Leu Ala Arg His Leu Arg Glu Glu Leu Gly Glu Thr Val Ala Gly
1700 1705 1710

Ala Pro Ala Thr Pro Val Thr Thr Val Ala Asp Ala Gly Glu Pro Ile
1715 1720 1725

Ala Ile Val Gly Met Ala Cys Arg Leu Pro Gly Gly Val Met Ser Pro

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1730	1735	1740	
Asp Asp Leu Trp Arg Met Val Ala Glu Gly Arg Asp Gly Met Ser Pro			
1745	1750	1755	1760
Phe Pro Gly Asp Arg Gly Trp Asp Leu Asp Gly Leu Phe Asp Ser Asp			
	1765	1770	1775
Pro Glu Arg Pro Gly Thr Ala Tyr Ile Arg Gln Gly Gly Phe Leu His			
	1780	1785	1790
Glu Ala Ala Leu Phe Asp Pro Gly Phe Phe Gly Ile Ser Pro Arg Glu			
	1795	1800	1805
Ala Leu Ala Met Asp Pro Gln Gln Arg Leu Leu Leu Glu Ala Ser Trp			
	1810	1815	1820
Glu Ala Leu Glu Arg Ala Gly Ile Asp Pro Thr Lys Ala Arg Gly Asp			
1825	1830	1835	1840
Ala Val Gly Val Phe Ser Gly Val Ser Ile His Asp Tyr Leu Glu Ser			
	1845	1850	1855
Leu Ser Asn Met Pro Ala Glu Leu Glu Gly Phe Val Thr Thr Ala Thr			
	1860	1865	1870
Ala Gly Ser Val Ala Ser Gly Arg Val Ser Tyr Thr Phe Gly Phe Glu			
	1875	1880	1885
Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser Ser Leu Val Ala			
	1890	1895	1900
Ile His Leu Ala Ala Gln Ala Leu Arg Gln Gly Glu Cys Thr Met Ala			
1905	1910	1915	1920
Leu Ala Gly Gly Val Ala Val Met Gly Ser Pro Ile Gly Val Ile Gly			
	1925	1930	1935

Met Ser Arg Gln Arg Gly Met Ala Glu Asp Gly Arg Val Lys Ala Phe
1940 1945 1950

Ala Asp Gly Ala Asp Gly Thr Val Leu Ser Glu Gly Val Gly Ile Val
1955 1960 1965

Val Leu Glu Arg Leu Ser Val Ala Arg Glu Arg Gly His Arg Val Leu
1970 1975 1980

Ala Val Leu Arg Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn Gly
1985 1990 1995 2000

Leu Thr Ala Pro Asn Gly Pro Ser Gln Gln Arg Val Ile Arg Ser Ala
2005 2010 2015

Leu Ala Gly Ala Gly Leu Gln Pro Ser Glu Val Asp Val Val Glu Ala
2020 2025 2030

His Gly Thr Gly Thr Ala Leu Gly Glu Pro Ile Glu Ala Gln Ala Leu
2035 2040 2045

Leu Ala Thr Tyr Gly Lys Ser Arg Glu Thr Pro Leu Trp Leu Gly Ser
2050 2055 2060

Leu Lys Ser Asn Ile Gly His Thr Gln Ala Ala Ala Gly Val Ala Ala
2065 2070 2075 2080

Val Ile Lys Met Val Gln Ala Leu Arg Gln Asp Thr Leu Pro Pro Thr
2085 2090 2095

Leu His Val Gln Glu Pro Thr Lys Gln Val Asp Trp Ser Ala Gly Ala
2100 2105 2110

Val Glu Leu Leu Thr Glu Gly Arg Glu Trp Ala Arg Asn Gly His Pro
2115 2120 2125

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Arg Arg Ala Gly Val Ser Ser Phe Gly Ile Ser Gly Thr Asn Ala His
2130 2135 2140

Leu Ile Leu Glu Glu Ala Pro Ala Asp Asp Thr Ala Glu Ala Asp Val
2145 2150 2155 2160

Pro Asp Ala Val Val Pro Val Val Ile Ser Ala Arg Ser Thr Gly Ser
2165 2170 2175

Leu Ala Gly Gln Ala Gly Arg Leu Ala Ala Phe Leu Asp Gly Asp Val
2180 2185 2190

Pro Leu Thr Arg Val Ala Gly Ala Leu Leu Ser Thr Arg Ala Thr Leu
2195 2200 2205

Thr Asp Arg Ala Val Val Val Ala Gly Ser Ala Glu Glu Ala Arg Ala
2210 2215 2220

Gly Leu Thr Ala Leu Ala Arg Gly Glu Ser Ala Ser Gly Leu Val Thr
2225 2230 2235 2240

Gly Thr Ala Gly Met Pro Gly Lys Thr Val Trp Val Phe Pro Gly Gln
2245 2250 2255

Gly Thr Gln Trp Ala Gly Met Gly Arg Glu Leu Leu Glu Ala Ser Pro
2260 2265 2270

Val Phe Ala Glu Arg Ile Glu Glu Cys Ala Ala Ala Leu Gln Pro Trp
2275 2280 2285

Ile Asp Trp Ser Leu Leu Asp Val Leu Arg Gly Glu Gly Glu Leu Asp
2290 2295 2300

Arg Val Asp Val Leu Gln Pro Ala Cys Phe Ala Val Met Val Gly Leu
2305 2310 2315 2320

Ala Ala Val Trp Ala Ser Val Gly Val Val Pro Asp Ala Val Leu Gly

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2325	2330	2335
His Ser Gln Gly Glu Ile Ala Ala Ala Cys Val Ser Gly Ala Leu Ser		
2340	2345	2350
Leu Glu Asp Ala Ala Lys Val Val Ala Leu Arg Ser Gln Ala Ile Ala		
2355	2360	2365
Ala Glu Leu Ser Gly Arg Gly Gly Met Ala Ser Ile Gln Leu Ser His		
2370	2375	2380
Asp Glu Val Ala Ala Arg Leu Ala Pro Trp Ala Gly Arg Val Glu Ile		
2385	2390	2395 2400
Ala Ala Val Asn Gly Pro Ala Ser Val Val Ile Ala Gly Asp Ala Glu		
2405	2410	2415
Ala Leu Thr Glu Ala Val Glu Val Leu Gly Gly Arg Arg Val Ala Val		
2420	2425	2430
Asp Tyr Ala Ser His Thr Arg His Val Glu Asp Ile Gln Asp Thr Leu		
2435	2440	2445
Ala Glu Thr Leu Ala Gly Ile Asp Ala Gln Ala Pro Val Val Pro Phe		
2450	2455	2460
Tyr Ser Thr Val Ala Gly Glu Trp Ile Thr Asp Ala Gly Val Val Asp		
2465	2470	2475 2480
Gly Gly Tyr Trp Tyr Arg Asn Leu Arg Asn Gln Val Gly Phe Gly Pro		
2485	2490	2495
Ala Val Ala Glu Leu Ile Glu Gln Gly His Gly Val Phe Val Glu Val		
2500	2505	2510
Ser Ala His Pro Val Leu Val Gln Pro Ile Ser Glu Leu Thr Asp Ala		
2515	2520	2525

Val Val Thr Gly Thr Leu Arg Arg Asp Asp Gly Gly Val Arg Arg Leu
2530 2535 2540

Leu Thr Ser Met Ala Glu Leu Phe Val Arg Gly Val Pro Val Asp Trp
2545 2550 2555 2560

Ala Thr Met Ala Pro Pro Ala Arg Val Glu Leu Pro Thr Tyr Ala Phe
2565 2570 2575

Asp His Gln His Phe Trp Leu Ser Pro Pro Ala Val Ala Asp Ala Pro
2580 2585 2590

Ala Leu Gly Leu Ala Gly Ala Asp His Pro Leu Leu Gly Ala Val Leu
2595 2600 2605

Pro Leu Pro Gln Ser Asp Gly Leu Val Phe Thr Ser Arg Leu Ser Val
2610 2615 2620

Arg Thr His Pro Trp Leu Ala Asp Gly Val Pro Ala Ala Ala Leu Val
2625 2630 2635 2640

Glu Leu Ala Val Arg Ala Gly Asp Glu Ala Gly Cys Pro Val Leu Ala
2645 2650 2655

Asp Leu Thr Val Glu Lys Leu Leu Val Leu Pro Glu Ser Gly Gly Leu
2660 2665 2670

Arg Val Gln Val Ile Val Ser Gly Glu Arg Thr Val Glu Val Tyr Ser
2675 2680 2685

Gln Leu Glu Gly Ala Glu Asp Trp Ile Arg Asn Ala Thr Gly His Leu
2690 2695 2700

Ser Ala Thr Ala Pro Ala His Glu Ala Phe Asp Phe Thr Ala Trp Pro
2705 2710 2715 2720

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Pro Ala Gly Ala Gln Gln Val Asp Gly Leu Trp Arg Arg Gly Asp Glu
2725 2730 2735

Ile Phe Ala Glu Val Ala Leu Pro Glu Glu Leu Asp Ala Gly Ala Phe
2740 2745 2750

Gly Ile His Pro Phe Leu Leu Asp Ala Ala Val Gln Pro Val Leu Ala
2755 2760 2765

Asp Asp Glu Gln Pro Ala Glu Trp Arg Ser Leu Val Leu His Ala Ala
2770 2775 2780

Gly Ala Ser Ala Leu Arg Val Arg Leu Val Pro Gly Gly Ala Leu Gln
2785 2790 2795 2800

Ala Ala Asp Glu Thr Gly Gly Leu Val Leu Thr Ala Asp Ser Val Ala
2805 2810 2815

Gly Arg Glu Leu Ser Ala Gly Lys Thr Arg Ala Gly Ser Leu Tyr Arg
2820 2825 2830

Val Asp Trp Thr Glu Val Ser Ile Ala Asp Ser Ala Val Pro Ala Asn
2835 2840 2845

Ile Glu Val Val Glu Ala Phe Gly Glu Glu Pro Leu Glu Leu Thr Gly
2850 2855 2860

Arg Val Leu Glu Ala Val Gln Thr Trp Leu Val Thr Ala Ala Asp Asp
2865 2870 2875 2880

Ala Arg Leu Val Val Val Thr Arg Gly Ala Val Arg Glu Val Thr Asp
2885 2890 2895

Pro Ala Gly Ala Ala Val Trp Gly Leu Val Arg Ala Ala Gln Ala Glu
2900 2905 2910

Asn Pro Gly Arg Ile Phe Leu Ile Asp Thr Asp Gly Glu Ile Pro Ala

2915	2920	2925
Leu Thr Gly Asp Glu Pro Glu Ile Ala Val Arg Gly Gly Lys Phe Phe		
2930	2935	2940
Val Pro Arg Ile Thr Arg Ala Glu Pro Ser Gly Ala Ala Val Phe Arg		
2945	2950	2955 2960
Pro Asp Gly Thr Val Leu Ile Ser Gly Ala Gly Ala Leu Gly Gly Leu		
2965	2970	2975
Val Ala Arg Arg Leu Val Glu Arg His Gly Val Arg Lys Leu Val Leu		
2980	2985	2990
Ala Ser Arg Arg Gly Arg Asp Ala Asp Gly Val Ala Asp Leu Val Ala		
2995	3000	3005
Asp Leu Ala Ala Asp Val Ser Val Val Ala Cys Asp Val Ser Asp Arg		
3010	3015	3020
Ala Gln Val Ala Ala Leu Leu Asp Glu His Arg Pro Thr Ala Val Val		
3025	3030	3035 3040
His Thr Ala Gly Val Ile Asp Ala Gly Val Ile Glu Thr Leu Asp Arg		
3045	3050	3055
Asp Arg Leu Ala Thr Val Phe Ala Pro Lys Val Asp Ala Val Arg His		
3060	3065	3070
Leu Asp Glu Leu Thr Arg Asp Arg Asp Leu Asp Ala Phe Val Val Tyr		
3075	3080	3085
Ser Ser Val Ser Ala Val Phe Met Gly Ala Gly Ser Gly Ser Tyr Ala		
3090	3095	3100
Ala Ala Asn Ala Phe Leu Asp Gly Leu Met Ala Asn Arg Arg Ala Ala		
3105	3110	3115 3120

Gly Leu Pro Gly Leu Ser Leu Ala Trp Gly Leu Trp Asp Gln Ser Thr

3125

3130

3135

Gly Met Ala Ala Gly Thr Asp Glu Ala Thr Arg Ala Arg Met Ser Arg

3140

3145

3150

Arg Gly Gly Leu Gln Ile Met Thr Gln Ala Glu Gly Met Asp Leu Phe

3155

3160

3165

Asp Ala Ala Leu Ser Ser Ala Glu Ser Leu Leu Val Pro Ala Lys Leu

3170

3175

3180

Asp Leu Arg Gly Val Arg Ala Asp Ala Ala Ala Gly Gly Val Val Pro

3185

3190

3195

3200

His Met Leu Arg Gly Leu Val Arg Ala Gly Arg Ala Gln Ala Arg Ala

3205

3210

3215

Ala Ser Thr Val Asp Asn Gly Leu Ala Gly Arg Leu Ala Gly Leu Ala

3220

3225

3230

Pro Ala Asp Gln Leu Thr Leu Leu Leu Asp Leu Val Arg Ala Gln Val

3235

3240

3245

Ala Ala Val Leu Gly His Ala Asp Ala Ser Ala Val Arg Val Asp Thr

3250

3255

3260

Ala Phe Lys Asp Ala Gly Phe Asp Ser Leu Thr Ala Val Glu Leu Arg

3265

3270

3275

3280

Asn Arg Met Arg Thr Ala Thr Gly Leu Lys Leu Pro Ala Thr Leu Val

3285

3290

3295

Phe Asp Tyr Pro Asn Pro Gln Ala Leu Ala Arg His Leu Arg Asp Glu

3300

3305

3310

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Leu Gly Gly Ala Ala Gln Thr Pro Val Thr Thr Ala Ala Ala Lys Ala
3315 3320 3325

Asp Leu Asp Glu Pro Ile Ala Ile Val Gly Met Ala Cys Arg Leu Pro
3330 3335 3340

Gly Gly Val Ala Gly Pro Glu Asp Leu Trp Arg Leu Val Ala Glu Gly
3345 3350 3355 3360

Arg Asp Ala Val Ser Ser Phe Pro Thr Asp Arg Gly Trp Asp Thr Asp
3365 3370 3375

Ser Leu Tyr Asp Pro Asp Pro Ala Arg Pro Gly Lys Thr Tyr Thr Arg
3380 3385 3390

His Gly Gly Phe Leu His Glu Ala Gly Leu Phe Asp Ala Gly Phe Phe
3395 3400 3405

Gly Ile Ser Pro Arg Glu Ala Val Ala Met Asp Pro Gln Gln Arg Leu
3410 3415 3420

Leu Leu Glu Ala Ser Trp Glu Ala Met Glu Asp Ala Gly Val Asp Pro
3425 3430 3435 3440

Leu Ser Leu Lys Gly Asn Asp Val Gly Val Phe Thr Gly Met Phe Gly
3445 3450 3455

Gln Gly Tyr Val Ala Pro Gly Asp Ser Val Val Thr Pro Glu Leu Glu
3460 3465 3470

Gly Phe Ala Gly Thr Gly Gly Ser Ser Ser Val Ala Ser Gly Arg Val
3475 3480 3485

Ser Tyr Val Phe Gly Phe Glu Gly Pro Ala Val Thr Ile Asp Ser Ala
3490 3495 3500

Cys Ser Ser Ser Leu Val Ala Met His Leu Ala Ala Gln Ser Leu Arg

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3505	3510	3515	3520
Gln Gly Glu Cys Ser Met Ala Leu Ala Gly Gly Ala Thr Val Met Ala			
3525	3530	3535	
Asn Pro Gly Ala Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala Val			
3540	3545	3550	
Asp Gly Arg Cys Lys Ala Phe Ala Ala Ala Ala Asp Gly Thr Gly Trp			
3555	3560	3565	
Ala Glu Gly Val Gly Val Val Ile Leu Glu Arg Leu Ser Val Ala Arg			
3570	3575	3580	
Glu Arg Gly His Arg Ile Leu Ala Val Leu Arg Gly Ser Ala Val Asn			
3585	3590	3595	3600
Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser Gln			
3605	3610	3615	
Gln Arg Val Ile Arg Arg Ala Leu Val Ser Ala Gly Leu Ala Pro Ser			
3620	3625	3630	
Asp Val Asp Val Val Glu Ala His Gly Thr Gly Thr Thr Leu Gly Asp			
3635	3640	3645	
Pro Ile Glu Ala Gln Ala Leu Leu Ala Thr Tyr Gly Lys Asp Arg Glu			
3650	3655	3660	
Ser Pro Leu Trp Leu Gly Ser Leu Lys Ser Asn Ile Gly His Ala Gln			
3665	3670	3675	3680
Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Gln Ala Leu Arg			
3685	3690	3695	
His Glu Val Leu Pro Pro Thr Leu His Val Asp Arg Pro Thr Pro Glu			
3700	3705	3710	

Val Asp Trp Ser Ala Gly Ala Val Glu Leu Leu Thr Glu Ala Arg Glu
3715 3720 3725

Trp Pro Arg Asn Gly Arg Pro Arg Arg Ala Gly Val Ser Ala Phe Gly
3730 3735 3740

Val Ser Gly Thr Asn Ala His Leu Ile Leu Glu Glu Ala Pro Ala Glu
3745 3750 3755 3760

Glu Pro Val Pro Thr Pro Glu Val Pro Leu Val Pro Val Val Val Ser
3765 3770 3775

Ala Arg Ser Arg Ala Ser Leu Ala Gly Gln Ala Gly Arg Leu Ala Gly
3780 3785 3790

Phe Val Ala Gly Asp Ala Ser Leu Ala Gly Val Ala Arg Ala Leu Val
3795 3800 3805

Thr Asn Arg Ala Ala Leu Thr Glu Arg Ala Val Met Val Val Gly Ser
3810 3815 3820

Arg Glu Glu Ala Val Thr Asn Leu Glu Ala Leu Ala Arg Gly Glu Asp
3825 3830 3835 3840

Pro Ala Ala Val Val Thr Gly Arg Ala Gly Ser Pro Gly Lys Leu Val
3845 3850 3855

Trp Val Phe Pro Gly Gln Gly Ser Gln Trp Ile Gly Met Gly Arg Glu
3860 3865 3870

Leu Leu Asp Ser Ser Pro Val Phe Ala Glu Arg Val Ala Glu Cys Ala
3875 3890 3885

Ala Ala Leu Glu Pro Trp Ile Asp Trp Ser Leu Leu Asp Val Leu Arg
3890 3895 3900

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Gly Glu Ser Asp Leu Leu Asp Arg Val Asp Val Val Gln Pro Ala Ser
3905 3910 3915 3920

Phe Ala Met Met Val Gly Leu Ala Ala Val Trp Gln Ser Val Gly Val
3925 3930 3935

Arg Pro Asp Ala Val Val Gly His Ser Gln Gly Glu Ile Ala Ala Ala
3940 3945 3950

Cys Val Ser Gly Ala Leu Ser Leu Gln Asp Ala Ala Lys Val Val Ala
3955 3960 3965

Leu Arg Ser Gln Ala Ile Ala Thr Arg Leu Ala Gly Arg Gly Gly Met
3970 3975 3980

Ala Ser Val Ala Leu Ser Glu Glu Asp Ala Thr Ala Trp Leu Ala Pro
3985 3990 3995 4000

Trp Ala Asp Arg Val Gln Val Ala Ala Val Asn Ser Pro Ala Ser Val
4005 4010 4015

Val Ile Ala Gly Glu Ala Gln Ala Leu Asp Glu Val Val Asp Ala Leu
4020 4025 4030

Ser Gly Gln Glu Val Arg Val Arg Arg Val Ala Val Asp Tyr Gly Ser
4035 4040 4045

His Thr Asn Gln Val Glu Ala Ile Glu Asp Leu Leu Ala Glu Thr Leu
4050 4055 4060

Ala Gly Ile Glu Ala Gln Ala Pro Lys Val Pro Phe Tyr Ser Thr Leu
4065 4070 4075 4080

Ile Gly Asp Trp Ile Arg Asp Ala Gly Ile Val Asp Gly Gly Tyr Trp
4085 4090 4095

Tyr Arg Asn Leu Arg Asn Gln Val Gly Phe Gly Pro Ala Val Ala Glu

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4100	4105	4110
Leu Val Arg Gln Gly His Gly Val Phe Val Glu Val Ser Ala His Pro		
4115	4120	4125
Val Leu Val Gln Pro Leu Ser Glu Leu Ser Asp Asp Ala Val Val Thr		
4130	4135	4140
Gly Ser Leu Arg Arg Glu Asp Gly Gly Leu Arg Arg Leu Leu Thr Ser		
4145	4150	4155
		4160
Met Ala Glu Leu Tyr Val Gln Gly Val Pro Leu Asp Trp Thr Ala Val		
4165	4170	4175
Leu Pro Arg Thr Gly Arg Val Asp Leu Pro Lys Tyr Ala Phe Asp His		
4180	4185	4190
Arg His Tyr Trp Leu Arg Pro Ala Glu Ser Ala Thr Asp Ala Ala Ser		
4195	4200	4205
Leu Gly Gln Ala Ala Ala Asp His Pro Leu Leu Gly Ala Val Val Glu		
4210	4215	4220
Leu Pro Gln Ser Asp Gly Leu Val Phe Thr Ser Arg Leu Ser Val Arg		
4225	4230	4235
		4240
Thr His Pro Trp Leu Ala Asp His Ala Val Gly Gly Val Val Ile Leu		
4245	4250	4255
Pro Gly Ser Gly Leu Ala Glu Leu Ala Val Arg Ala Gly Asp Glu Ala		
4260	4265	4270
Gly Cys Thr Ala Leu Asp Glu Leu Ile Ile Glu Ala Pro Leu Val Val		
4275	4280	4285
Pro Ala Gln Gly Ala Val Arg Val Gln Val Ala Leu Ser Gly Pro Asp		
4290	4295	4300

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Glu Thr Gly Ser Arg Thr Val Asp Leu Tyr Ser Gln Arg Asp Gly Gly
4305 4310 4315 4320

Ala Gly Thr Trp Thr Arg His Ala Thr Gly Val Leu Ser Thr Ala Pro
 4325 4330 4335

Ala Gln Glu Pro Glu Phe Asp Phe His Ala Trp Pro Pro Ala Asp Ala
 4340 4345 4350

Glu Arg Ile Asp Val Glu Thr Phe Tyr Thr Asp Leu Ala Glu Arg Gly
 4355 4360 4365

Tyr Gly Tyr Gly Pro Ala Phe Gln Gly Leu Gln Ala Val Trp Arg Arg
 4370 4375 4380

Asp Gly Asp Val Phe Ala Glu Val Ala Leu Pro Glu Asp Leu Arg Lys
4385 4390 4395 4400

Asp Ala Gly Arg Phe Gly Val His Pro Ala Leu Leu Asp Ala Ala Leu
 4405 4410 4415

Gln Ala Ala Thr Ala Val Gly Gly Asp Glu Pro Gly Gln Pro Val Leu
 4420 4425 4430

Ala Phe Ala Trp Asn Gly Leu Val Leu His Ala Ala Gly Ala Ser Ala
 4435 4440 4445

Leu Arg Val Arg Leu Ala Pro Ser Gly Pro Asp Thr Leu Ser Val Ala
 4450 4455 4460

Ala Ala Asp Glu Thr Gly Gly Leu Val Leu Thr Met Glu Ser Leu Val
4465 4470 4475 4480

Ser Arg Pro Val Ser Ala Glu Gln Leu Gly Ala Ala Ala Asp Ala Gly
 4485 4490 4495

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His Asp Ala Met Phe Arg Val Asp Trp Thr Glu Leu Pro Ala Val Pro
 4500 4505 4510

Arg Ala Glu Leu Pro Pro Trp Val Arg Ile Asp Thr Ala Asp Asp Val
 4515 4520 4525

Ala Ala Leu Ala Glu Lys Ala Asp Ala Pro Pro Val Val Val Trp Glu
 4530 4535 4540

Ala Ala Gly Gly Asp Pro Ala Leu Ala Val Ser Ser Arg Val Leu Glu
 4545 4550 4555 4560

Ile Met Gln Ala Trp Leu Ala Ala Pro Ala Phe Glu Glu Ala Arg Leu
 4565 4570 4575

Val Val Thr Thr Arg Gly Ala Val Pro Ala Gly Gly Asp His Thr Leu
 4580 4585 4590

Thr Asp Pro Ala Ala Ala Ala Val Trp Gly Leu Val Arg Ser Ala Gln
 4595 4600 4605

Ala Glu His Pro Asp Arg Val Val Leu Leu Asp Thr Asp Gly Glu Val
 4610 4615 4620

Pro Leu Gly Ala Val Leu Ala Ser Gly Glu Pro Gln Leu Ala Val Arg
 4625 4630 4635 4640

Gly Thr Thr Phe Phe Val Pro Arg Leu Ala Arg Ala Thr Arg Leu Ser
 4645 4650 4655

Asp Ala Pro Pro Ala Phe Asp Pro Asp Gly Thr Val Leu Val Ser Gly
 4660 4665 4670

Ala Gly Ser Leu Gly Thr Leu Val Ala Arg His Leu Val Thr Arg His
 4675 4680 4685

Gly Val Arg Arg Val Val Leu Ala Ser Arg Gln Gly Arg Asp Ala Glu

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4690	4695	4700
Gly Ala Gln Asp Leu Ile Thr Glu Leu Thr Gly Glu Gly Ala Asp Val		
4705	4710	4715 4720
Ser Phe Val Ala Cys Asp Val Ser Asp Arg Asp Gln Val Ala Ala Leu		
4725	4730	4735
Leu Ala Gly Leu Pro Asp Leu Thr Gly Val Val His Thr Ala Gly Val		
4740	4745	4750
Phe Glu Asp Gly Val Ile Glu Ala Leu Thr Pro Asp Gln Leu Ala Asn		
4755	4760	4765
Val Tyr Ala Ala Lys Val Thr Ala Ala Met His Leu Asp Glu Leu Thr		
4770	4775	4780
Arg Asp Arg Asp Leu Gly Ala Phe Val Val Phe Ser Ser Val Ala Gly		
4785	4790	4795 4800
Val Met Gly Gly Gly Gly Gln Gly Pro Tyr Ala Ala Ala Asn Ala Phe		
4805	4810	4815
Leu Asp Ala Ala Met Ala Ser Arg Gln Ala Ala Gly Leu Pro Gly Leu		
4820	4825	4830
Ser Leu Ala Trp Gly Leu Trp Glu Arg Ser Ser Gly Met Ala Ala His		
4835	4840	4845
Leu Ser Glu Val Asp His Ala Arg Ala Ser Arg Asn Gly Val Leu Glu		
4850	4855	4860
Leu Thr Arg Ala Glu Gly Leu Ala Leu Phe Asp Leu Gly Leu Arg Met		
4865	4870	4875 4880
Ala Glu Ser Leu Leu Val Pro Ile Lys Leu Asp Leu Ala Ala Met Arg		
4885	4890	4895

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Ala Ser Thr Val Pro Val Leu Phe Arg Gly Leu Val Arg Pro Ser Arg
 4900 4905 4910

Thr Gln Ala Arg Thr Ala Ser Thr Val Asp Arg Gly Leu Ala Gly Arg
 4915 4920 4925

Leu Ala Gly Leu Pro Val Ala Glu Arg Ala Ala Val Leu Val Asp Leu
 4930 4935 4940

Val Arg Gly Gln Val Ala Val Val Leu Gly Tyr Asp Gly Pro Glu Ala
 4945 4950 4955 4960

Val Arg Pro Asp Thr Ala Phe Lys Asp Thr Gly Phe Asp Ser Leu Thr
 4965 4970 4975

Ser Val Glu Leu Arg Asn Arg Leu Arg Glu Ala Thr Gly Leu Lys Leu
 4980 4985 4990

Pro Ala Thr Leu Val Phe Asp Tyr Pro Asn Pro Leu Ala Val Ala Arg
 4995 5000 5005

Tyr Leu Gly Ala Arg Leu Val Pro Asp Gly Thr Ala Asn Gly Asn Gly
 5010 5015 5020

Asn Gly Asn Gly His Ser Glu Asp Asp Arg Leu Arg His Ala Leu Ala
 5025 5030 5035 5040

Ala Ile Ala Ala Glu Asp Ala Gly Glu Glu Arg Ser Ile Ala Asp Leu
 5045 5050 5055

Gly Val Asp Asp Leu Val Gln Leu Ala Phe Gly Asp Glu
 5060 5065

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1721 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Met Ala Cys Arg Leu Pro Gly Gly Val Thr Gly Pro Gly Asp Leu Trp
1 5 10 15

Arg Leu Val Ala Glu Gly Gly Asp Ala Val Ser Gly Phe Pro Thr Asp
20 25 30

Arg Cys Trp Asp Leu Asp Thr Leu Phe Asp Pro Asp Pro Asp His Ala
35 40 45

Gly Thr Ser Tyr Thr Asp Gln Gly Gly Phe Leu His Asp Ala Ala Leu
50 55 60

Phe Asp Pro Gly Phe Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met
65 70 75 80

Asp Pro Gln Gln Arg Leu Leu Leu Glu Ala Ser Trp Glu Ala Leu Glu
85 90 95

Gly Val Gly Leu Asp Pro Ala Ser Leu Gln Gly Thr Asp Val Gly Val
100 105 110

Phe Thr Gly Ala Gly Gly Ser Gly Tyr Gly Gly Gly Leu Thr Gly Pro
115 120 125

Glu Met Gln Ser Phe Ala Gly Thr Gly Leu Ala Ser Ser Val Ala Ser

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130	135	140																	
Gly	Arg	Val	Ser	Tyr	Val	Phe	Gly	Phe	Glu	Gly	Pro	Ala	Val	Thr	Ile				
145					150					155					160				
Asp	Thr	Ala	Cys	Ser	Ser	Ser	Leu	Val	Ala	Met	His	Leu	Ala	Ala	Gln				
				165					170						175				
Ala	Leu	Arg	Gln	Gly	Asp	Cys	Ser	Met	Ala	Leu	Ala	Gly	Gly	Ala	Met				
			180					185					190						
Val	Met	Ser	Gly	Pro	Asp	Ser	Phe	Val	Val	Phe	Ser	Arg	Gln	Arg	Gly				
		195					200					205							
Leu	Ala	Thr	Asp	Gly	Arg	Cys	Lys	Ala	Phe	Ala	Ser	Gly	Ala	Asp	Gly				
210					215							220							
Met	Val	Leu	Ala	Glu	Gly	Ile	Ser	Val	Val	Val	Leu	Glu	Arg	Leu	Ser				
225				230						235					240				
Val	Ala	Arg	Glu	Arg	Gly	His	Arg	Val	Leu	Ala	Val	Leu	Arg	Gly	Ser				
				245					250					255					
Ala	Val	Asn	Gln	Asp	Gly	Ala	Ser	Asn	Gly	Leu	Thr	Ala	Pro	Asn	Gly				
			260					265						270					
Pro	Ser	Gln	Gln	Arg	Val	Ile	Arg	Ala	Ala	Leu	Ala	Asn	Ala	Gly	Ile				
		275					280					285							
Gly	Pro	Ser	Asp	Val	Asp	Leu	Val	Glu	Ala	His	Gly	Thr	Gly	Thr	Ser				
290					295						300								
Leu	Gly	Asp	Pro	Ile	Glu	Ala	Gln	Ala	Leu	Leu	Ala	Thr	Tyr	Gly	Gln				
305				310						315					320				
Asp	Arg	Glu	Thr	Pro	Leu	Trp	Leu	Gly	Ser	Leu	Lys	Ser	Asn	Ile	Gly				
				325				330						335					

His Thr Gln Ala Ala Ala Gly Val Ala Ser Val Ile Lys Val Val Gln
 340 345 350

Ala Leu Arg His Gly Val Met Pro Pro Thr Leu His Val Asp Glu Pro
 355 360 365

Ser Ser Gln Val Asp Trp Ser Glu Gly Ala Val Glu Leu Leu Thr Gly
 370 375 380

Ser Arg Asp Trp Pro Arg Gly Asp Arg Pro Arg Arg Ala Gly Val Ser
 385 390 395 400

Ser Phe Gly Val Ser Gly Thr Asn Val His Leu Ile Ile Glu Glu Ala
 405 410 415

Pro Glu Glu Pro Ala Ala Ala Val Pro Thr Ser Ala Asp Val Val Pro
 420 425 430

Leu Val Val Ser Ala Arg Ser Thr Gly Ser Leu Ala Gly Gln Ala Asp
 435 440 445

Arg Leu Thr Glu Val Asp Val Pro Leu Gly His Leu Ala Gly Ala Leu
 450 455 460

Val Ala Gly Arg Ala Val Leu Glu Glu Arg Ala Val Val Val Ala Gly
 465 470 475 480

Ser Ala Glu Glu Ala Arg Ala Gly Leu Gly Ala Leu Ala Arg Gly Glu
 485 490 495

Ala Ala Pro Gly Val Val Thr Gly Thr Ala Gly Lys Pro Gly Lys Val
 500 505 510

Val Trp Val Phe Pro Gly Gln Gly Thr Gln Trp Val Gly Met Gly Arg
 515 520 525

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Glu Leu Leu Asp Ala Ser Pro Val Phe Ala Glu Arg Ile Lys Glu Cys
 530 535 540

Ala Ala Ala Leu Asp Gln Trp Thr Asp Trp Ser Leu Leu Asp Val Leu
 545 550 555 560

Arg Gly Asp Gly Asp Leu Asp Ser Val Glu Val Leu Gln Pro Ala Cys
 565 570 575

Phe Ala Val Met Val Gly Leu Ala Ala Val Trp Glu Ser Ala Gly Val
 580 585 590

Arg Pro Asp Ala Val Val Gly His Ser Gln Gly Glu Ile Ala Ala Ala
 595 600 605

Cys Val Ser Gly Ala Leu Thr Leu Asp Asp Ala Ala Lys Val Val Ala
 610 615 620

Leu Arg Ser Gln Ala Ile Ala Ala Arg Leu Ser Gly Arg Gly Gly Met
 625 630 635 640

Ala Ser Val Ala Leu Ser Glu Asp Glu Ala Asn Ala Arg Leu Gly Leu
 645 650 655

Trp Asp Gly Arg Ile Glu Val Ala Ala Val Asn Gly Pro Ala Ser Val
 660 665 670

Val Ile Ala Gly Asp Ala Gln Ala Leu Asp Glu Ala Leu Glu Val Leu
 675 680 685

Ala Gly Asp Gly Val Arg Val Arg Gln Val Ala Val Asp Tyr Ala Ser
 690 695 700

His Thr Arg His Val Glu Asp Ile Arg Asp Thr Leu Ala Glu Thr Leu
 705 710 715 720

Ala Gly Ile Thr Ala Gln Ala Pro Asp Val Pro Phe Arg Ser Thr Val

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725	730	735
Thr Gly Gly Trp Val Arg Asp Ala Asp Val Leu Asp Gly Gly Tyr Trp		
740	745	750
Tyr Arg Asn Leu Arg Asn Gln Val Arg Phe Gly Pro Ala Val Ala Glu		
755	760	765
Leu Leu Glu Gln Gly His Gly Val Phe Val Glu Val Ser Ala His Pro		
770	775	780
Val Leu Val Gln Pro Ile Ser Glu Leu Thr Asp Ala Val Val Thr Gly		
785	790	795
800		
Thr Leu Arg Arg Asp Asp Gly Gly Leu Arg Arg Leu Leu Thr Ser Met		
805	810	815
Ala Glu Leu Phe Val Arg Gly Val Arg Val Asp Trp Ala Thr Leu Val		
820	825	830
Pro Pro Ala Arg Val Asp Leu Pro Thr Tyr Ala Phe Asp His Gln His		
835	840	845
Phe Trp Leu Arg Pro Ala Ala Gln Ala Asp Ala Val Ser Leu Gly Gln		
850	855	860
Ala Ala Ala Glu His Pro Leu Leu Gly Ala Val Val Arg Leu Pro Gln		
865	870	875
880		
Ser Asp Gly Leu Val Phe Thr Ser Arg Leu Ser Leu Arg Thr His Pro		
885	890	895
Trp Leu Ala Asp His Thr Ile Gly Gly Val Val Leu Phe Pro Gly Thr		
900	905	910
Gly Leu Val Glu Leu Ala Val Arg Ala Gly Asp Glu Ala Gly Cys Pro		
915	920	925

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Val Leu Asp Glu Leu Val Thr Glu Ala Pro Leu Val Val Pro Gly Gln

930

935

940

Gly Gly Val Asn Val Gln Val Thr Val Ser Gly Pro Asp Gln Asn Gly

945

950

955

960

Leu Arg Thr Val Asp Ile His Ser Gln Arg Asp Asp Val Trp Thr Arg

965

970

975

His Ala Thr Gly Thr Val Ser Ala Thr Pro Ala Ser Ser Pro Gly Phe

980

985

990

Asp Phe Thr Ala Trp Pro Pro Pro Asp Gly Gln Arg Val Glu Ile Gly

995

1000

1005

Asp Phe Tyr Ala Asp Leu Ala Glu Arg Gly Tyr Ala Tyr Gly Pro Leu

1010

1015

1020

Phe Gln Gly Val Arg Ala Val Trp Gln Arg Gly Glu Asp Val Phe Ala

1025

1030

1035

1040

Glu Val Ala Leu Pro Glu Asp Arg Arg Glu Asp Ala Ala Arg Phe Gly

1045

1050

1055

Leu His Pro Ala Leu Leu Asp Ala Ala Leu Gln Thr Gly Thr Ile Ala

1060

1065

1070

Ala Ala Ala Ser Gly Gln Pro Gly Lys Ser Val Met Pro Phe Ser Trp

1075

1080

1085

Asn Arg Leu Ala Leu His Ala Val Gly Ala Ala Gly Leu Arg Val Arg

1090

1095

1100

Val Ala Pro Gly Gly Pro Asp Ala Leu Thr Val Glu Ala Ala Asp Glu

1105

1110

1115

1120

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Thr Gly Ala Pro Val Leu Thr Met Asp Ser Leu Ile Leu Arg Glu Val
1125 1130 1135

Ala Leu Asp Gln Leu Asp Thr Ala Arg Ala Gly Ser Leu Tyr Arg Val
1140 1145 1150

Asp Trp Thr Pro Leu Pro Thr Val Asp Ser Ala Val Pro Ala Gly Arg
1155 1160 1165

Ala Glu Val Leu Glu Ala Phe Gly Glu Glu Pro Leu Asp Leu Thr Gly
1170 1175 1180

Arg Val Leu Ala Ala Leu Gln Ala Trp Leu Ser Asp Ala Ala Glu Glu
1185 1190 1195 1200

Ala Arg Leu Val Val Val Thr Arg Gly Ala Val Pro Ala Gly Asp Gly
1205 1210 1215

Val Val Ser Asp Pro Ala Gly Ala Ala Val Trp Gly Leu Val Arg Ala
1220 1225 1230

Ala Gln Ala Glu Asn Pro Asp Arg Phe Val Leu Leu Asp Thr Asp Gly
1235 1240 1245

Glu Val Pro Leu Glu Ala Val Leu Ala Thr Gly Glu Pro Gln Leu Ala
1250 1255 1260

Leu Arg Gly Thr Thr Phe Ser Val Pro Arg Leu Ala Arg Val Thr Glu
1265 1270 1275 1280

Pro Ala Glu Ala Pro Leu Thr Phe Arg Pro Asp Gly Thr Val Leu Val
1285 1290 1295

Ser Gly Ala Gly Thr Leu Gly Ala Leu Ala Ala Arg Asp Leu Val Thr
1300 1305 1310

Arg His Gly Val Arg Arg Leu Val Leu Ala Ser Arg Arg Gly Arg Ala

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1315	1320	1325
Ala Glu Gly Ile Asp Asp Leu Val Ala Glu Leu Thr Gly His Gly Ala		
1330	1335	1340
Glu Val Thr Val Ala Ala Cys Asp Val Ser Asp Arg Asp Gln Val Ala		
1345	1350	1355 1360
Ala Leu Leu Lys Glu His Ala Leu Thr Ala Val Val His Thr Ala Gly		
1365	1370	1375
Val Phe Asp Ala Gly Val Thr Gly Ala Leu Thr Arg Glu Arg Leu Ala		
1380	1385	1390
Lys Val Phe Ala Pro Lys Val Asp Ala Ala Asn His Leu Asp Glu Leu		
1395	1400	1405
Thr Arg Asp Leu Asp Leu Asp Ala Phe Ile Val Tyr Ser Ser Ala Ser		
1410	1415	1420
Ser Ile Phe Met Gly Ala Gly Ser Gly Gly Tyr Ala Ala Ala Asn Ala		
1425	1430	1435 1440
Tyr Leu Asp Gly Leu Met Ala Ala Arg Arg Ala Ala Gly Leu Pro Gly		
1445	1450	1455
Leu Ser Leu Ala Trp Gly Pro Trp Glu Gln Leu Thr Gly Met Ala Asp		
1460	1465	1470
Thr Ile Asp Asp Leu Thr Leu Ala Arg Met Ser Arg Arg Glu Gly Arg		
1475	1480	1485
Gly Gly Val Arg Ala Leu Gly Ser Ala Asp Gly Met Glu Leu Phe Asp		
1490	1495	1500
Ala Ala Leu Ala Ala Gly Gln Ala Leu Leu Val Pro Ile Glu Leu Asp		
1505	1510	1515 1520

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Leu Arg Glu Val Arg Ala Asp Ala Ala Gly Gly Gly Thr Val Pro His

1525

1530

1535

Leu Leu Arg Gly Leu Val Arg Ala Gly Arg Gln Ala Ala Arg Thr Ala

1540

1545

1550

Ala Thr Glu Asp Gly Gly Leu Glu Arg Arg Leu Ala Gly Leu Thr Val

1555

1560

1565

Ala Glu Gln Glu Ala Leu Leu Leu Asp Leu Val Arg Gly Gln Val Ala

1570

1575

1580

Val Val Leu Gly His Ala Asp Ser Ser Gly Val Arg Ala Asp Ala Ala

1585

1590

1595

1600

Phe Lys Asp Ala Gly Phe Asp Ser Leu Thr Ser Val Glu Leu Arg Asn

1605

1610

1615

Arg Leu Arg Glu Thr Thr Gly Leu Lys Leu Pro Ala Thr Leu Val Phe

1620

1625

1630

Asp His Pro Asn Pro Leu Ala Leu Ala Arg His Leu Arg Ala Glu Leu

1635

1640

1645

Ala Val Asp Glu Ala Ser Pro Ala Asp Ala Val Leu Ala Gly Leu Ala

1650

1655

1660

Gly Leu Glu Ala Ala Ile Ala Ala Ala Gly Ala Pro Asp Gly Asp Arg

1665

1670

1675

1680

Ile Thr Ala Arg Leu Arg Glu Leu Leu Lys Ala Ala Glu Ala Ala Glu

1685

1690

1695

Ala Arg Pro Gly Thr Ser Gly Asp Leu Asp Thr Ala Ser Asp Glu Glu

1700

1705

1710

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Leu Phe Ala Leu Val Asp Gly Leu Asp
 1715 1720

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1688 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

Met Ala Cys Arg Tyr Pro Gly Gly Val Ser Ser Pro Glu Asp Leu Trp
 1 5 10 15

Arg Leu Val Ala Glu Gly Thr Asp Ala Val Ser Ala Phe Pro Gly Asp
 20 25 30

Arg Gly Trp Asp Val Asp Gly Leu Val Asp Pro Asp Pro Asp Arg Pro
 35 40 45

Gly Thr Thr Tyr Thr Asp Gln Gly Gly Phe Leu His Glu Ala Gly Leu
 50 55 60

Phe Asp Ala Gly Phe Phe Gly Ile Ser Pro Arg Glu Ala Val Ala Met
 65 70 75 80

Asp Pro Gln Gln Arg Leu Leu Leu Glu Thr Ser Trp Glu Ala Ile Glu
 85 90 95

Arg Thr Gly Thr Asp Pro Leu Ser Leu Lys Gly Ser Asp Ile Gly Val

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100	105	110
Phe Thr Gly Val Ala Ser Met Gly Tyr Gly Ala Gly Gly Gly Val Val		
115	120	125
Ala Pro Glu Leu Glu Gly Phe Val Gly Thr Gly Ala Ala Pro Cys Ile		
130	135	140
Ala Ser Gly Arg Val Ser Tyr Val Leu Gly Phe Glu Gly Pro Ala Val		
145	150	155
		160
Thr Val Asp Thr Gly Cys Ser Ser Ser Leu Val Ala Met His Leu Ala		
165	170	175
Ala Gln Ala Leu Arg Arg Gly Glu Cys Ser Met Ala Leu Ala Gly Gly		
180	185	190
Ala Met Val Met Ala Gln Pro Gly Ser Phe Val Ser Phe Ser Arg Gln		
195	200	205
Arg Gly Leu Ala Leu Asp Gly Arg Cys Lys Ala Phe Ser Asp Ser Ala		
210	215	220
Asp Gly Met Gly Leu Ala Glu Gly Val Gly Val Ile Ala Leu Glu Arg		
225	230	235
		240
Leu Ser Val Ala Arg Glu Arg Gly His Arg Val Leu Ala Val Leu Arg		
245	250	255
Gly Ile Ala Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro		
260	265	270
Asn Gly Pro Ser Gln Gln Arg Val Ile Arg Ala Ala Leu Ala Glu Ala		
275	280	285
Gly Leu Ser Pro Ser Asp Val Asp Ala Val Glu Gly His Gly Thr Gly		
290	295	300

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Thr Thr Leu Gly Asp Pro Ile Glu Ala Gln Ala Leu Leu Ala Thr Tyr
305 310 315 320

Gly Lys Gly Arg Asp Pro Glu Lys Pro Leu Trp Leu Gly Ser Val Lys
325 330 335

Ser Asn Leu Gly His Thr Gln Ala Ala Ala Gly Val Ala Ser Val Ile
340 345 350

Lys Met Val Gln Ala Leu Arg His Gly Val Leu Pro Pro Thr Leu His
355 360 365

Val Asp Arg Pro Ser Thr Glu Val Asp Trp Ser Ala Gly Ala Val Ser
370 375 380

Leu Leu Thr Glu Ala Arg Glu Trp Pro Arg Glu Gly Arg Pro Arg Arg
385 390 395 400

Ala Gly Val Ser Ser Phe Gly Ile Ser Gly Thr Asn Ala His Leu Ile
405 410 415

Leu Glu Glu Ala Pro Glu Glu Glu Pro Pro Val Ala Glu Ala Pro Ser
420 425 430

Ala Gly Val Val Pro Val Val Val Ser Ala Arg Gly Ala Leu Ala Gly
435 440 445

Gln Ala Gly Arg Leu Ala Ala Phe Leu Glu Ala Ser Asp Glu Pro Leu
450 455 460

Val Thr Val Ala Gly Ala Leu Ile Cys Gly Arg Ser Arg Phe Gly Asp
465 470 475 480

Arg Ala Val Val Val Ala Gly Thr Arg Ala Glu Ala Thr Ala Gly Leu
485 490 495

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Ala Ala Leu Ala Arg Gly Glu Ser Ala Ala Asp Val Val Thr Gly Thr
 500 505 510

Val Ala Ala Ser Gly Val Pro Gly Lys Leu Val Trp Val Phe Pro Gly
 515 520 525

Gln Gly Ser Gln Trp Val Gly Met Gly Arg Glu Leu Leu Glu Ala Ser
 530 535 540

Pro Val Phe Ala Ala Arg Ile Ala Glu Cys Ala Ala Ala Leu Glu Pro
 545 550 555 560

Trp Ile Asp Trp Ser Leu Leu Asp Val Leu Arg Gly Glu Gly Asp Leu
 565 570 575

Asp Arg Val Asp Val Val Gln Pro Ala Ser Phe Ala Val Met Val Gly
 580 585 590

Leu Ala Ala Val Trp Ser Ser Val Gly Val Val Pro Asp Ala Val Leu
 595 600 605

Gly His Ser Gln Gly Glu Ile Ala Ala Ala Cys Val Ser Gly Ala Leu
 610 615 620

Ser Leu Gln Asp Ala Ala Lys Val Val Ala Leu Arg Ser Gln Ala Ile
 625 630 635 640

Ala Ala Lys Leu Ala Gly Arg Gly Gly Met Ala Ser Val Ala Leu Ser
 645 650 655

Glu Glu Asp Ala Val Ala Arg Leu Arg His Trp Ala Asp Arg Val Glu
 660 665 670

Val Ala Ala Val Asn Ser Pro Ser Ser Val Val Ile Ala Gly Asp Ala
 675 680 685

Glu Ala Leu Asp Gln Ala Leu Glu Ala Leu Thr Gly Gln Asp Ile Arg

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690	695	700
Val Arg Arg Val Ala Val Asp Tyr Ala Ser His Thr Arg His Val Glu		
705	710	715 720
Asp Ile Gln Glu Pro Leu Ala Glu Ala Leu Ala Gly Ile Glu Ala His		
725	730	735
Ala Pro Thr Leu Pro Phe Phe Ser Thr Leu Thr Gly Asp Trp Ile Arg		
740	745	750
Glu Ala Gly Val Val Asp Gly Gly Tyr Trp Tyr Arg Asn Leu Arg Asn		
755	760	765
Gln Val Gly Phe Gly Pro Ala Val Ala Glu Leu Leu Gly Leu Gly His		
770	775	780
Arg Val Phe Val Glu Val Ser Ala His Pro Val Leu Val Gln Ala Ile		
785	790	795 800
Ser Ala Ile Ala Asp Asp Thr Asp Ala Val Val Thr Gly Ser Leu Arg		
805	810	815
Arg Glu Glu Gly Gly Leu Arg Arg Leu Leu Thr Ser Met Ala Glu Leu		
820	825	830
Phe Val Arg Gly Val Asp Val Asp Trp Ala Thr Met Val Pro Pro Ala		
835	840	845
Arg Val Asp Leu Pro Thr Tyr Ala Phe Asp His Gln His Tyr Trp Leu		
850	855	860
Arg Tyr Val Glu Thr Ala Thr Asp Ala Ala Gly Pro Val Val Arg Leu		
865	870	875 880
Pro Gln Thr Gly Gly Leu Val Phe Thr Thr Glu Trp Ser Leu Lys Ser		
885	890	895

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Gln Pro Trp Leu Ala Glu His Thr Leu Glu Asp Leu Val Val Val Pro
 900 905 910

Gly Ala Ala Leu Val Glu Leu Ala Val Arg Ala Gly Asp Glu Ala Gly
 915 920 925

Thr Pro Val Leu Asp Glu Leu Val Ile Glu Thr Pro Leu Val Val Pro
 930 935 940

Glu Arg Gly Ala Ile Arg Val Gln Val Thr Val Ser Gly Pro Asp Asp
 945 950 955 960

Gly Thr Arg Thr Leu Glu Val His Ser Gln Pro Glu Asp Ala Thr Asp
 965 970 975

Glu Trp Thr Arg His Ala Thr Gly Thr Leu Ser Ala Thr Pro Asp Glu
 980 985 990

Ser Ser Gly Phe Asp Phe Thr Ala Trp Pro Pro Pro Gly Ala Arg Gln
 995 1000 1005

Leu Asp Gly Val Pro Ala Ile Trp Arg Ala Gly Asp Glu Ile Phe Ala
 1010 1015 1020

Glu Val Ser Leu Pro Asp Asp Ala Asp Ala Glu Ala Phe Gly Ile His
 1025 1030 1035 1040

Pro Ala Leu Leu Asp Ala Ala Leu His Pro Ala Leu Pro Gly Asp Asp
 1045 1050 1055

Gly Leu Thr Gln Pro Met Glu Trp Arg Gly Leu Thr Leu His Ala Ala
 1060 1065 1070

Gly Ala Ser Thr Leu Arg Val Arg Leu Val Pro Gly Gly Phe Leu Glu
 1075 1080 1085

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Ala Ala Asp Gly Ala Gly Ser Leu Val Val Thr Ala Lys Glu Val Ala
1090 1095 1100

Leu Arg Pro Val Thr Ile Ala Arg Ser Arg Thr Thr Thr Arg Asp Ser
1105 1110 1115 1120

Leu Phe Gln Leu Asn Trp Ile Glu Leu Pro Glu Ser Gly Val Val Ala
1125 1130 1135

Ala Ala Asp Asp Thr Glu Val Leu Glu Val Pro Ala Gly Asp Ser Pro
1140 1145 1150

Leu Ala Ala Thr Ser Arg Val Leu Glu Arg Leu Gln Thr Trp Leu Thr
1155 1160 1165

Glu Pro Glu Ala Glu Gln Leu Val Val Val Thr Arg Gly Ala Val Pro
1170 1175 1180

Ala Gly Asp Thr Pro Val Thr Asp Pro Ala Ala Ala Val Trp Gly
1185 1190 1195 1200

Leu Val Arg Ser Ala Gln Ala Glu Asn Pro Asp Arg Ile Val Leu Leu
1205 1210 1215

Asp Thr Asp Gly Glu Val Pro Leu Gly Ala Val Leu Ala Gly Gly Glu
1220 1225 1230

Pro Gln Val Ala Val Arg Gly Thr Ala Leu Tyr Val Pro Arg Leu Ala
1235 1240 1245

Arg Ala Asp Ala Ala Pro Val Ser Gly Leu His Gly Thr Val Leu Val
1250 1255 1260

Ser Gly Ala Gly Val Leu Gly Glu Ile Val Ala Arg His Leu Val Thr
1265 1270 1275 1280

Arg His Gly Val Arg Lys Leu Val Leu Ala Ser Arg Arg Gly Leu Asp

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1285	1290	1295
Ala Asp Gly Ala Lys Asp Leu Val Thr Asp Leu Thr Gly Glu Gly Ala		
1300	1305	1310
Asp Val Ser Val Val Ala Cys Asp Leu Ala Asp Arg Asn Gln Val Ala		
1315	1320	1325
Ala Leu Leu Ala Asp His Arg Pro Ala Ser Val Ile His Thr Ala Gly		
1330	1335	1340
Val Leu Asp Asp Gly Val Ile Gly Thr Leu Thr Pro Glu Arg Leu Ala		
1345	1350	1355
		1360
Lys Val Phe Ala Pro Lys Val Asp Ala Val Arg His Leu Asp Glu Leu		
1365	1370	1375
Thr Arg Asp Leu Asp Leu Asp Ala Phe Val Val Phe Ser Ser Gly Ser		
1380	1385	1390
Gly Val Phe Gly Ser Pro Gly Gln Gly Asn Tyr Ala Ala Ala Asn Ala		
1395	1400	1405
Phe Leu Asp Ala Ala Met Ala Ser Arg Arg Ala Ala Gly Leu Pro Gly		
1410	1415	1420
Leu Ser Leu Ala Trp Gly Leu Trp Glu Gln Ala Thr Gly Met Thr Ala		
1425	1430	1435
		1440
His Leu Gly Gly Thr Asp Gln Ala Arg Met Ser Arg Gly Gly Val Arg		
1445	1450	1455
Pro Ile Thr Ala Glu Glu Gly Met Ala Leu Phe Asp Thr Ala Leu Gly		
1460	1465	1470
Ala Gln Pro Ala Leu Leu Val Pro Val Lys Leu Asp Leu Arg Glu Val		
1475	1480	1485

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Arg Ala Gly Gly Ala Val Pro His Leu Leu Arg Gly Leu Val Arg Ala
1490 1495 1500

Gly Arg Arg Gln Ala Gln Ala Ala Ser Thr Val Asp Asn Gln Leu Leu
1505 1510 1515 1520

Gly Arg Leu Ala Gly Leu Gly Ala Pro Glu Gln Glu Ala Leu Leu Val
1525 1530 1535

Asp Leu Val Arg Gly Gln Val Ala Ala Val Leu Gly His Ala Gly Pro
1540 1545 1550

Asp Ala Val Arg Ala Asp Thr Ala Phe Lys Asp Ala Gly Phe Asp Ser
1555 1560 1565

Leu Thr Ser Val Asp Leu Arg Asn Arg Leu Arg Glu Ser Thr Gly Leu
1570 1575 1580

Lys Leu Pro Ala Thr Leu Ala Phe Asp Tyr Pro Thr Pro Leu Val Leu
1585 1590 1595 1600

Ala Arg His Leu Arg Asp Glu Leu Gly Ala Gly Asp Asp Ala Leu Ser
1605 1610 1615

Val Val His Ala Arg Leu Glu Asp Val Glu Ala Leu Leu Gly Gly Leu
1620 1625 1630

Arg Leu Asp Glu Ser Thr Lys Thr Gly Leu Thr Leu Arg Leu Gln Gly
1635 1640 1645

Leu Val Ala Arg Cys Asn Gly Val Asn Asp Gln Thr Gly Gly Glu Thr
1650 1655 1660

Leu Ala Asp Arg Leu Glu Ala Ala Ser Ala Asp Glu Val Leu Asp Phe
1665 1670 1675 1680

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Ile Asp Glu Glu Leu Gly Leu Thr
1685

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3413 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Met Ala Thr Asp Glu Lys Leu Leu Lys Tyr Leu Lys Arg Val Thr Ala
1 5 10 15

Glu Leu His Ser Leu Arg Lys Gln Gly Ala Arg His Ala Asp Glu Pro
20 25 30

Leu Ala Val Val Gly Met Ala Cys Arg Phe Pro Gly Gly Val Ser Ser
35 40 45

Pro Glu Asp Leu Trp Gln Leu Val Ala Gly Gly Val Asp Ala Leu Ser
50 55 60

Asp Phe Pro Asp Asp Arg Gly Trp Glu Leu Asp Gly Leu Phe Asp Pro
65 70 75 80

Asp Pro Asp His Pro Gly Thr Ser Tyr Thr Ser Gln Gly Gly Phe Leu
85 90 95

Arg Gly Ala Gly Leu Phe Asp Ala Gly Leu Phe Gly Ile Ser Pro Arg

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100	105	110
Glu Ala Leu Val Met Asp Pro Gln Gln Arg Val Leu Leu Glu Thr Ser		
115	120	125
Trp Glu Ala Leu Glu Asp Ala Gly Val Asp Pro Leu Ser Leu Lys Gly		
130	135	140
Ser Asp Val Gly Val Phe Ser Gly Val Phe Thr Gln Gly Tyr Gly Ala		
145	150	155
160		
Gly Ala Ile Thr Pro Asp Leu Glu Ala Phe Ala Gly Ile Gly Ala Ala		
165	170	175
Ser Ser Val Ala Ser Gly Arg Val Ser Tyr Val Phe Gly Leu Glu Gly		
180	185	190
Pro Ala Val Thr Ile Asp Thr Ala Cys Ser Ser Ser Leu Val Ala Ile		
195	200	205
His Leu Ala Ala Gln Ala Leu Arg Ala Gly Glu Cys Ser Met Ala Leu		
210	215	220
Ala Gly Gly Ala Thr Val Met Pro Thr Pro Gly Thr Phe Val Ala Phe		
225	230	235
240		
Ser Arg Gln Arg Val Leu Ala Ala Asp Gly Arg Ser Lys Ala Phe Ser		
245	250	255
Ser Thr Ala Asp Gly Thr Gly Trp Ala Glu Gly Ala Gly Val Leu Val		
260	265	270
Leu Glu Arg Leu Ser Val Ala Gln Glu Arg Gly His Arg Ile Leu Ala		
275	280	285
Val Leu Arg Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn Gly Leu		
290	295	300

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Thr Ala Pro Asn Gly Pro Ser Gln Gln Arg Val Ile Arg Lys Ala Leu
305 310 315 320

Ala Gly Ala Gly Leu Val Ala Ser Asp Val Asp Val Val Glu Ala His
325 330 335

Gly Thr Gly Thr Ala Leu Gly Asp Pro Ile Glu Ala Gln Ala Leu Leu
340 345 350

Ala Thr Tyr Gly Gln Gly Arg Glu Arg Pro Leu Trp Leu Gly Ser Val
355 360 365

Lys Ser Asn Phe Gly His Thr Gln Ala Ala Ala Gly Val Ala Gly Val
370 375 380

Ile Lys Met Val Gln Ala Leu Arg His Gly Ala Met Pro Pro Thr Leu
385 390 395 400

His Val Ala Glu Pro Thr Pro Glu Val Asp Trp Ser Ala Gly Ala Val
405 410 415

Glu Leu Leu Thr Glu Pro Arg Glu Trp Pro Ala Gly Asp Arg Pro Arg
420 425 430

Arg Ala Gly Val Ser Ala Phe Gly Ile Ser Gly Thr Asn Ala His Leu
435 440 445

Ile Leu Glu Glu Ala Pro Pro Ala Asp Ala Val Ala Glu Glu Pro Glu
450 455 460

Phe Lys Gly Pro Val Pro Leu Val Val Ser Ala Gly Ser Pro Thr Ser
465 470 475 480

Leu Ala Ala Gln Ala Gly Arg Leu Ala Glu Val Leu Ala Ser Gly Gly
485 490 495

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Val Ser Arg Ala Arg Leu Ala Ser Gly Leu Leu Ser Gly Arg Ala Leu
500 505 510

Leu Gly Asp Arg Ala Val Val Val Ala Gly Thr Asp Glu Asp Ala Val
515 520 525

Ala Gly Leu Arg Ala Leu Ala Arg Gly Asp Arg Ala Pro Gly Val Leu
530 535 540

Thr Gly Ser Ala Lys His Gly Lys Val Val Tyr Val Phe Pro Gly Gln
545 550 555 560

Gly Ser Gln Arg Leu Gly Met Gly Arg Glu Leu Tyr Asp Arg Tyr Pro
565 570 575

Val Phe Ala Thr Ala Phe Asp Glu Ala Cys Glu Gln Leu Asp Val Cys
580 585 590

Leu Ala Gly Arg Ala Gly His Arg Val Arg Asp Val Val Leu Gly Glu
595 600 605

Val Pro Ala Glu Thr Gly Leu Leu Asn Gln Thr Val Phe Thr Gln Ala
610 615 620

Gly Leu Phe Ala Val Glu Ser Ala Leu Phe Arg Leu Ala Glu Ser Trp
625 630 635 640

Gly Val Arg Pro Asp Val Val Leu Gly His Ser Ile Gly Glu Ile Thr
645 650 655

Ala Ala Tyr Ala Ala Gly Val Phe Ser Leu Pro Asp Ala Ala Arg Ile
660 665 670

Val Ala Ala Arg Gly Arg Leu Met Gln Ala Leu Ala Pro Gly Gly Ala
675 680 685

Met Val Ala Val Ala Ala Ser Glu Ala Glu Val Ala Glu Leu Leu Gly

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690	695	700
Asp Gly Val Glu Leu Ala Ala Val Asn Gly Pro Ser Ala Val Val Leu		
705	710	715 720
Ser Gly Asp Ala Asp Ala Val Val Ala Ala Ala Ala Arg Met Arg Glu		
	725	730 735
Arg Gly His Lys Thr Lys Gln Leu Lys Val Ser His Ala Phe His Ser		
	740	745 750
Ala Arg Met Ala Pro Met Leu Ala Glu Phe Ala Ala Glu Leu Ala Gly		
	755	760 765
Val Thr Trp Arg Glu Pro Glu Ile Pro Val Val Ser Asn Val Thr Gly		
	770	775 780
Arg Phe Ala Glu Pro Gly Glu Leu Thr Glu Pro Gly Tyr Trp Ala Glu		
	785	790 795 800
His Val Arg Arg Pro Val Arg Phe Ala Glu Gly Val Ala Ala Ala Thr		
	805	810 815
Glu Ser Gly Gly Ser Leu Phe Val Glu Leu Gly Pro Gly Ala Ala Leu		
	820	825 830
Thr Ala Leu Val Glu Glu Thr Ala Glu Val Thr Cys Val Ala Ala Leu		
	835	840 845
Arg Asp Asp Arg Pro Glu Val Thr Ala Leu Ile Thr Ala Val Ala Glu		
	850	855 860
Leu Phe Val Arg Gly Val Ala Val Asp Trp Pro Ala Leu Leu Pro Pro		
	865	870 875 880
Val Thr Gly Phe Val Asp Leu Pro Lys Tyr Ala Phe Asp Gln Gln His		
	885	890 895

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Tyr Trp Leu Gln Pro Ala Ala Gln Ala Thr Asp Ala Ala Ser Leu Gly
 900 905 910

Gln Val Ala Ala Asp His Pro Leu Leu Gly Ala Val Val Arg Leu Pro
 915 920 925

Gln Ser Asp Gly Leu Val Phe Thr Ser Arg Leu Ser Leu Lys Ser His
 930 935 940

Pro Trp Leu Ala Asp His Val Ile Gly Gly Val Val Leu Val Ala Gly
 945 950 955 960

Thr Gly Leu Val Glu Leu Ala Val Arg Ala Gly Asp Glu Ala Gly Cys
 965 970 975

Pro Val Leu Glu Glu Leu Val Ile Glu Ala Pro Leu Val Val Pro Asp
 980 985 990

His Gly Gly Val Arg Ile Gln Val Val Val Gly Ala Pro Gly Glu Thr
 995 1000 1005

Gly Ser Arg Ala Val Glu Val Tyr Ser Leu Arg Glu Asp Ala Gly Ala
 1010 1015 1020

Glu Val Trp Ala Arg His Ala Thr Gly Phe Leu Ala Ala Thr Pro Ser
 1025 1030 1035 1040

Gln His Lys Pro Phe Asp Phe Thr Ala Trp Pro Pro Pro Gly Val Glu
 1045 1050 1055

Arg Val Asp Val Glu Asp Phe Tyr Asp Gly Leu Val Asp Arg Gly Tyr
 1060 1065 1070

Ala Tyr Gly Pro Ser Phe Arg Gly Leu Arg Ala Val Trp Arg Arg Gly
 1075 1080 1085

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Asp Glu Val Phe Ala Glu Val Ala Leu Ala Glu Asp Asp Arg Ala Asp
1090 1095 1100

Ala Ala Arg Phe Gly Ile His Pro Gly Leu Leu Asp Ala Ala Leu His
1105 1110 1115 1120

Ala Gly Met Ala Gly Ala Thr Thr Thr Glu Glu Pro Gly Arg Pro Val
1125 1130 1135

Leu Pro Phe Ala Trp Asn Gly Leu Val Leu His Ala Ala Gly Ala Ser
1140 1145 1150

Ala Leu Arg Val Arg Leu Ala Pro Ser Gly Pro Asp Ala Leu Ser Val
1155 1160 1165

Glu Ala Ala Asp Glu Ala Gly Gly Leu Val Val Thr Ala Asp Ser Leu
1170 1175 1180

Val Ser Arg Pro Val Ser Ala Glu Gln Leu Gly Ala Ala Ala Asn His
1185 1190 1195 1200

Asp Ala Leu Phe Arg Val Glu Trp Thr Glu Ile Ser Ser Ala Gly Asp
1205 1210 1215

Val Pro Ala Asp His Val Glu Val Leu Glu Ala Val Gly Glu Asp Pro
1220 1225 1230

Leu Glu Leu Thr Gly Arg Val Leu Glu Ala Val Gln Thr Trp Leu Ala
1235 1240 1245

Asp Ala Ala Asp Asp Ala Arg Leu Val Val Val Thr Arg Gly Ala Val
1250 1255 1260

His Glu Val Thr Asp Pro Ala Gly Ala Ala Val Trp Gly Leu Ile Arg
1265 1270 1275 1280

Ala Ala Gln Ala Glu Asn Pro Asp Arg Ile Val Leu Leu Asp Thr Asp

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1285	1290	1295
Gly Glu Val Pro Leu Gly Arg Val Leu Ala Thr Gly Glu Pro Gln Thr		
1300	1305	1310
Ala Val Arg Gly Ala Thr Leu Phe Ala Pro Arg Leu Ala Arg Ala Glu		
1315	1320	1325
Ala Ala Glu Ala Pro Ala Val Thr Gly Gly Thr Val Leu Ile Ser Gly		
1330	1335	1340
Ala Gly Ser Leu Gly Ala Leu Thr Ala Arg His Leu Val Ala Arg His		
1345	1350	1355
		1360
Gly Val Arg Arg Leu Val Leu Val Ser Arg Arg Gly Pro Asp Ala Asp		
1365	1370	1375
Gly Met Ala Glu Leu Thr Ala Glu Leu Ile Ala Gln Gly Ala Glu Val		
1380	1385	1390
Ala Val Val Ala Cys Asp Leu Ala Asp Arg Asp Gln Val Arg Val Leu		
1395	1400	1405
Leu Ala Glu His Arg Pro Asn Ala Val Val His Thr Ala Gly Val Leu		
1410	1415	1420
Asp Asp Gly Val Phe Glu Ser Leu Thr Arg Glu Arg Leu Ala Lys Val		
1425	1430	1435
		1440
Phe Ala Pro Lys Val Thr Ala Ala Asn His Leu Asp Glu Leu Thr Arg		
1445	1450	1455
Glu Leu Asp Leu Arg Ala Phe Val Val Phe Ser Ser Ala Ser Gly Val		
1460	1465	1470
Phe Gly Ser Ala Gly Gln Gly Asn Tyr Ala Ala Ala Asn Ala Tyr Leu		
1475	1480	1485

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Asp Ala Val Val Ala Asn Arg Arg Ala Ala Gly Leu Pro Gly Thr Ser

1490

1495

1500

Leu Ala Trp Gly Leu Trp Glu Gln Thr Asp Gly Met Thr Ala His Leu

1505

1510

1515

1520

Gly Asp Ala Asp Gln Ala Arg Ala Ser Arg Gly Gly Val Leu Ala Ile

1525

1530

1535

Ser Pro Ala Glu Gly Met Glu Leu Phe Asp Ala Ala Pro Asp Gly Leu

1540

1545

1550

Val Val Pro Val Lys Leu Asp Leu Arg Lys Thr Arg Ala Gly Gly Thr

1555

1560

1565

Val Pro His Leu Leu Arg Gly Leu Val Arg Pro Gly Arg Gln Gln Ala

1570

1575

1580

Arg Pro Ala Ser Thr Val Asp Asn Gly Leu Ala Gly Arg Leu Ala Gly

1585

1590

1595

1600

Leu Ala Pro Ala Glu Gln Glu Ala Leu Leu Leu Asp Val Val Arg Thr

1605

1610

1615

Gln Val Ala Leu Val Leu Gly His Ala Gly Pro Glu Ala Val Arg Ala

1620

1625

1630

Asp Thr Ala Phe Lys Asp Thr Gly Phe Asp Ser Leu Thr Ser Val Glu

1635

1640

1645

Leu Arg Asn Arg Leu Arg Glu Ala Ser Gly Leu Lys Leu Pro Ala Thr

1650

1655

1660

Leu Val Phe Asp Tyr Pro Thr Pro Val Ala Leu Ala Arg Tyr Leu Arg

1665

1670

1675

1680

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Asp Glu Leu Gly Asp Thr Val Ala Thr Thr Pro Val Ala Thr Ala Ala
 1685 1690 1695

Ala Ala Asp Ala Gly Glu Pro Ile Ala Ile Val Gly Met Ala Cys Arg
 1700 1705 1710

Leu Pro Gly Gly Val Thr Asp Pro Glu Gly Leu Trp Arg Leu Val Arg
 1715 1720 1725

Asp Gly Leu Glu Gly Leu Ser Pro Phe Pro Glu Asp Arg Gly Trp Asp
 1730 1735 1740

Leu Glu Asn Leu Phe Asp Asp Asp Pro Asp Arg Ser Gly Thr Thr Tyr
 1745 1750 1755 1760

Thr Ser Arg Gly Gly Phe Leu Asp Gly Ala Gly Leu Phe Asp Ala Gly
 1765 1770 1775

Phe Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln
 1780 1785 1790

Arg Leu Leu Leu Glu Ala Ala Trp Glu Ala Leu Glu Gly Thr Gly Val
 1795 1800 1805

Asp Pro Gly Ser Leu Lys Gly Ala Asp Val Gly Val Phe Ala Gly Val
 1810 1815 1820

Ser Asn Gln Gly Tyr Gly Met Gly Ala Asp Pro Ala Glu Leu Ala Gly
 1825 1830 1835 1840

Tyr Ala Ser Thr Ala Gly Ala Ser Ser Val Val Ser Gly Arg Val Ser
 1845 1850 1855

Tyr Val Phe Gly Phe Glu Gly Pro Ala Val Thr Ile Asp Thr Ala Cys
 1860 1865 1870

Ser Ser Ser Leu Val Ala Met His Leu Ala Gly Gln Ala Leu Arg Gln

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1875	1880	1885
Gly Glu Cys Ser Met Ala Leu Ala Gly Gly Val Thr Val Met Gly Thr		
1890	1895	1900
Pro Gly Thr Phe Val Glu Phe Ala Lys Gln Arg Gly Leu Ala Gly Asp		
1905	1910	1915 1920
Gly Arg Cys Lys Ala Tyr Ala Glu Gly Ala Asp Gly Thr Gly Trp Ala		
1925	1930	1935
Glu Gly Val Gly Val Val Val Leu Glu Arg Leu Ser Val Ala Arg Glu		
1940	1945	1950
Arg Gly His Arg Val Leu Ala Val Leu Arg Gly Ser Ala Val Asn Ser		
1955	1960	1965
Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser Gln Gln		
1970	1975	1980
Arg Val Ile Arg Arg Ala Leu Ala Gly Ala Gly Leu Glu Pro Ser Asp		
1985	1990	1995 2000
Val Asp Ile Val Glu Gly His Gly Thr Gly Thr Ala Leu Gly Asp Pro		
2005	2010	2015
Ile Glu Ala Gln Ala Leu Leu Ala Thr Tyr Gly Lys Asp Arg Asp Pro		
2020	2025	2030
Glu Thr Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Phe Gly His Thr		
2035	2040	2045
Gln Ser Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Gln Ala Leu		
2050	2055	2060
Arg His Gly Val Met Pro Pro Thr Leu His Val Asp Arg Pro Thr Ser		
2065	2070	2075 2080

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Gln Val Asp Trp Ser Ala Gly Ala Val Glu Val Leu Thr Glu Ala Arg

2085

2090

2095

Glu Trp Pro Arg Asn Gly Arg Pro Arg Arg Ala Gly Val Ser Ser Phe

2100

2105

2110

Gly Ile Ser Gly Thr Asn Ala His Leu Ile Ile Glu Glu Ala Pro Ala

2115

2120

2125

Glu Pro Gln Leu Ala Gly Pro Pro Pro Asp Gly Gly Val Val Pro Leu

2130

2135

2140

Val Val Ser Ala Arg Ser Pro Gly Ala Leu Ala Gly Gln Ala Arg Arg

2145

2150

2155

2160

Leu Ala Thr Phe Leu Gly Asp Gly Pro Leu Ser Asp Val Ala Gly Ala

2165

2170

2175

Leu Thr Ser Arg Ala Leu Phe Gly Glu Arg Ala Val Val Val Ala Asp

2180

2185

2190

Ser Ala Glu Glu Ala Arg Ala Gly Leu Gly Ala Leu Ala Arg Gly Glu

2195

2200

2205

Asp Ala Pro Gly Leu Val Arg Gly Arg Val Pro Ala Ser Gly Leu Pro

2210

2215

2220

Gly Lys Leu Val Trp Val Phe Pro Gly Gln Gly Thr Gln Trp Val Gly

2225

2230

2235

2240

Met Gly Arg Glu Leu Leu Glu Glu Ser Pro Val Phe Ala Glu Arg Ile

2245

2250

2255

Ala Glu Cys Ala Ala Ala Leu Glu Pro Trp Ile Gly Trp Ser Leu Phe

2260

2265

2270

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Asp Val Leu Arg Gly Asp Gly Asp Leu Asp Arg Val Asp Val Leu Gln
2275 2280 2285

Pro Ala Cys Phe Ala Val Met Val Gly Leu Ala Ala Val Trp Ser Ser
2290 2295 2300

Ala Gly Val Val Pro Asp Ala Val Leu Gly His Ser Gln Gly Glu Ile
2305 2310 2315 2320

Ala Ala Ala Cys Val Ser Gly Ala Leu Ser Leu Glu Asp Ala Ala Lys
2325 2330 2335

Val Val Ala Leu Arg Ser Gln Ala Ile Ala Ala Lys Leu Ser Gly Arg
2340 2345 2350

Gly Gly Met Ala Ser Val Ala Leu Gly Glu Ala Asp Val Val Ser Arg
2355 2360 2365

Leu Ala Asp Gly Val Glu Val Ala Ala Val Asn Gly Pro Ala Ser Val
2370 2375 2380

Val Ile Ala Gly Asp Ala Gln Ala Leu Asp Glu Thr Leu Glu Ala Leu
2385 2390 2395 2400

Ser Gly Ala Gly Ile Arg Ala Arg Arg Val Ala Val Asp Tyr Ala Ser
2405 2410 2415

His Thr Arg His Val Glu Asp Ile Glu Asp Thr Leu Ala Glu Ala Leu
2420 2425 2430

Ala Gly Ile Asp Ala Arg Ala Pro Leu Val Pro Phe Leu Ser Thr Leu
2435 2440 2445

Thr Gly Glu Trp Ile Arg Asp Glu Gly Val Val Asp Gly Gly Tyr Trp
2450 2455 2460

Tyr Arg Asn Leu Arg Gly Arg Val Arg Phe Gly Pro Ala Val Glu Ala

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2465	2470	2475	2480
Leu Leu Ala Gln Gly His Gly Val Phe Val Glu Leu Ser Ala His Pro			
2485	2490	2495	
Val Leu Val Gln Pro Ile Thr Glu Leu Thr Asp Glu Thr Ala Ala Val			
2500	2505	2510	
Val Thr Gly Ser Leu Arg Arg Asp Asp Gly Gly Leu Arg Arg Leu Leu			
2515	2520	2525	
Thr Ser Met Ala Glu Leu Phe Val Arg Gly Val Glu Val Asp Trp Thr			
2530	2535	2540	
Ser Leu Val Pro Pro Ala Arg Ala Asp Leu Pro Thr Tyr Ala Phe Asp			
2545	2550	2555	2560
His Glu His Tyr Trp Leu Arg Ala Ala Asp Thr Ala Ser Asp Ala Val			
2565	2570	2575	
Ser Leu Gly Leu Ala Gly Ala Asp His Pro Leu Leu Gly Ala Val Val			
2580	2585	2590	
Gln Leu Pro Gln Ser Asp Gly Leu Val Phe Thr Ser Arg Leu Ser Leu			
2595	2600	2605	
Arg Ser His Pro Trp Leu Ala Asp His Ala Val Arg Asp Val Val Ile			
2610	2615	2620	
Val Pro Gly Thr Gly Leu Val Glu Leu Ala Val Arg Ala Gly Asp Glu			
2625	2630	2635	2640
Ala Gly Cys Pro Val Leu Asp Glu Leu Val Ile Glu Ala Pro Leu Val			
2645	2650	2655	
Val Pro Arg Arg Gly Gly Val Arg Val Gln Val Ala Leu Gly Gly Pro			
2660	2665	2670	

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Ala Asp Asp Gly Ser Arg Thr Val Asp Val Phe Ser Leu Arg Glu Asp

2675

2680

2685

Ala Asp Ser Trp Leu Arg His Ala Thr Gly Val Leu Val Pro Glu Asn

2690

2695

2700

Arg Pro Arg Gly Thr Ala Ala Phe Asp Phe Ala Ala Trp Pro Pro Pro

2705

2710

2715

2720

Glu Ala Lys Pro Val Asp Leu Thr Gly Ala Tyr Asp Val Leu Ala Asp

2725

2730

2735

Val Gly Tyr Gly Tyr Gly Pro Thr Phe Arg Ala Val Arg Ala Val Trp

2740

2745

2750

Arg Arg Gly Ser Gly Asn Thr Thr Glu Thr Phe Ala Glu Ile Ala Leu

2755

2760

2765

Pro Glu Asp Ala Arg Ala Glu Ala Gly Arg Phe Gly Ile His Pro Ala

2770

2775

2780

Leu Leu Asp Ala Ala Leu His Ser Thr Met Val Ser Ala Ala Ala Asp

2785

2790

2795

2800

Thr Glu Ser Tyr Gly Asp Glu Val Arg Leu Pro Phe Ala Trp Asn Gly

2805

2810

2815

Leu Arg Leu His Ala Ala Gly Ala Ser Val Leu Arg Val Arg Val Ala

2820

2825

2830

Lys Pro Glu Arg Asp Ser Leu Ser Leu Glu Ala Val Asp Glu Ser Gly

2835

2840

2845

Gly Leu Val Val Thr Leu Asp Ser Leu Val Gly Arg Pro Val Ser Asn

2850

2855

2860

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Asp Gln Leu Thr Thr Ala Ala Gly Pro Ala Gly Ala Gly Ser Leu Tyr
2865 2870 2875 2880

Arg Val Asp Trp Thr Pro Leu Ser Ser Val Asp Thr Ser Gly Arg Val
2885 2890 2895

Pro Ser Trp Leu Pro Val Ala Thr Ala Glu Glu Val Ala Thr Leu Ala
2900 2905 2910

Asp Asp Val Leu Thr Gly Ala Thr Glu Ala Pro Ala Val Ala Val Met
2915 2920 2925

Glu Ala Val Ala Asp Glu Gly Ser Val Leu Ala Leu Thr Val Arg Val
2930 2935 2940

Leu Asp Val Val Gln Cys Trp Leu Ala Gly Gly Gly Leu Glu Gly Thr
2945 2950 2955 2960

Lys Leu Ala Ile Val Thr Arg Gly Ala Val Pro Ala Gly Asp Gly Val
2965 2970 2975

Val His Asp Pro Ala Ala Ala Ala Val Trp Gly Leu Val Arg Ala Ala
2980 2985 2990

Gln Ala Glu Asn Pro Asp Arg Ile Val Leu Leu Asp Val Glu Pro Glu
2995 3000 3005

Ala Asp Val Pro Pro Leu Leu Gly Ser Val Leu Ala Asp Gly Glu Pro
3010 3015 3020

Gln Val Ala Val Arg Gly Thr Thr Leu Ser Ile Pro Arg Leu Ala Arg
3025 3030 3035 3040

Ala Ala Arg Pro Asp Pro Ala Ala Gly Phe Lys Thr Arg Gly Pro Val
3045 3050 3055

Leu Val Thr Gly Gly Thr Gly Ser Leu Gly Gly Leu Val Ala Arg His

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3060	3065	3070
Leu Val Glu Arg His Gly Val Arg Gln Leu Val Leu Ala Ser Arg Arg		
3075	3080	3085
Gly Leu Asp Ala Glu Gly Ala Lys Asp Leu Val Thr Asp Leu Thr Ala		
3090	3095	3100
Leu Gly Ala Asp Val Ala Val Ala Ala Cys Asp Val Ala Asp Arg Asp		
3105	3110	3115 3120
Gln Val Ala Ala Leu Leu Thr Glu His Arg Pro Ser Ala Val Val His		
3125	3130	3135
Thr Ala Gly Val Pro Asp Ala Gly Val Ile Gly Thr Val Thr Pro Asp		
3140	3145	3150
Arg Leu Ala Glu Val Phe Ala Pro Lys Val Thr Ala Ala Arg His Leu		
3155	3160	3165
Asp Glu Leu Thr Arg Asp Leu Asp Leu Asp Ser Phe Val Val Tyr Ser		
3170	3175	3180
Ser Val Ser Ala Val Phe Met Gly Ala Gly Ser Gly Ser Tyr Ala Ala		
3185	3190	3195 3200
Ala Asn Ala Tyr Leu Asp Gly Leu Met Ala His Arg Arg Ala Ala Gly		
3205	3210	3215
Leu Pro Gly Gln Ser Leu Ala Trp Gly Leu Trp Asp Gln Thr Thr Gly		
3220	3225	3230
Gly Met Ala Ala Gly Thr Asp Glu Ala Gly Arg Ala Arg Met Thr Arg		
3235	3240	3245
Arg Gly Gly Leu Val Ala Met Lys Pro Ala Ala Gly Leu Asp Leu Phe		
3250	3255	3260

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Asp Ala Ala Ile Gly Ser Gly Glu Pro Leu Leu Val Pro Ala Gln Leu
 3265 3270 3275 3280

Asp Leu Arg Gly Leu Arg Ala Glu Ala Ala Gly Gly Thr Glu Val Pro
 3285 3290 3295

His Leu Leu Arg Gly Leu Val Arg Ala Gly Arg Gln Gln Ala Arg Ala
 3300 3305 3310

Ala Ser Thr Val Glu Glu Asn Trp Ala Gly Arg Leu Ala Gly Leu Glu
 3315 3320 3325

Pro Ala Glu Arg Gly Gln Val Leu Leu Glu Leu Val Arg Ala Gln Val
 3330 3335 3340

Ala Gly Val Leu Gly Tyr Arg Ala Ala His Gln Val Asp Pro Asp Gln
 3345 3350 3355 3360

Gly Leu Phe Glu Ile Gly Phe Asp Ser Leu Thr Ala Ile Glu Leu Arg
 3365 3370 3375

Asn Arg Leu Arg Ala Arg Thr Glu Arg Lys Ile Ser Pro Gly Val Val
 3380 3385 3390

Phe Asp His Pro Thr Pro Ala Leu Leu Ala Ala His Leu Asn Glu Leu
 3395 3400 3405

Leu Arg Lys Lys Val
 3410

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 226 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Met	Ala	Ile	Pro	Tyr	Ser	Ser	Leu	Ala	Tyr	Glu	Leu	Arg	Asp	Ala	Val
1					5				10					15	

Asn	Val	Val	Asp	Leu	Asp	Glu	Asp	Asp	Val	Phe	Val	Thr	Ser	Ile	Ala
			20					25						30	

Glu	Gly	Gln	Gly	Gly	Ala	Cys	Tyr	His	Leu	Asn	Arg	Leu	Phe	His	Arg
			35					40						45	

Leu	Leu	Thr	Glu	Leu	Gly	Tyr	Asp	Val	Thr	Pro	Leu	Ala	Gly	Ser	Thr
			50				55					60			

Ala	Glu	Gly	Arg	Glu	Thr	Phe	Gly	Thr	Asp	Val	Glu	His	Met	Phe	Asn
			65				70				75			80	

Leu	Val	Thr	Leu	Asp	Gly	Ala	Asp	Trp	Leu	Val	Asp	Val	Gly	Tyr	Pro
				85				90						95	

Gly	Pro	Thr	Tyr	Val	Glu	Pro	Leu	Ala	Val	Ser	Pro	Ala	Val	Gln	Thr
				100				105						110	

Gln	Tyr	Gly	Ser	Gln	Phe	Arg	Leu	Val	Glu	Gln	Glu	Thr	Gly	Tyr	Ala
				115				120						125	

Leu	Gln	Arg	Arg	Gly	Ala	Val	Thr	Arg	Trp	Ser	Val	Val	Tyr	Thr	Phe
				130				135						140	

Thr	Thr	Gln	Pro	Arg	Gln	Trp	Ser	Asp	Trp	Lys	Glu	Leu	Glu	Asp	Asn
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145 150 155 160

Phe Arg Ala Leu Val Gly Asp Thr Thr Arg Thr Asp Thr Gln Glu Thr
165 170 175

Leu Cys Gly Arg Ala Phe Ala Asn Gly Gln Val Phe Leu Arg Gln Arg
180 185 190

Arg Tyr Leu Thr Val Glu Asn Gly Arg Glu Gln Val Arg Thr Ile Thr
195 200 205


Asp Asp Asp Glu Phe Arg Ala Leu Val Ser Arg Val Leu Ser Gly Asp
210 215 220

His Gly
225

Ciba-Geigy AG

CH-4002 Basel

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM	
Identification reference given by the DEPOSITOR: pRi7-3	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM 11114
II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION	
The microorganism identified under I. above was accompanied by: <input checked="" type="checkbox"/> (X) a scientific description <input checked="" type="checkbox"/> (X) a proposed taxonomic designation (Mark with a cross where applicable).	
III. RECEIPT AND ACCEPTANCE	
This International Depositary Authority accepts the microorganism identified under I. above, which was received by it on 1996-08-10 (Date of the original deposit) ¹ .	
IV. RECEIPT OF REQUEST FOR CONVERSION	
The microorganism identified under I above was received by this International Depositary Authority on (date of original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion).	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s):  Date: 1996-08-14


¹ Where Rule 6.4 (d) applies, such date is the date on which the status of international depositary authority was acquired.

Ciba-Geigy AG

CH-4002 Basel

VIABILITY STATEMENT

issued pursuant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: Ciba-Geigy AG Address: CH-4002 Basel	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM 11114 Date of the deposit or the transfer ¹ : 1996-08-10
III. VIABILITY STATEMENT	
The viability of the microorganism identified under II above was tested on 1996-08-12 ¹ . On that date, the said microorganism was (X) ² viable () ³ no longer viable	
IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED ⁴	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s):  Date: 1996-08-14

¹ Indicate the date of original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).

² In the cases referred to in Rule 10.2(a) (ii) and (iii), refer to the most recent viability test.


³ Mark with a cross the applicable box.

⁴ Fill in if the information has been requested and if the results of the test were negative.

Novartis AG

CH-4002 Basel

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM	
Identification reference given by the DEPOSITOR: pRi44-2	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM 11655
II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION	
<p>The microorganism identified under I. above was accompanied by:</p> <p>(X) a scientific description (X) a proposed taxonomic designation</p> <p>(Mark with a cross where applicable).</p>	
III. RECEIPT AND ACCEPTANCE	
<p>This International Depositary Authority accepts the microorganism identified under I. above, which was received by it on 1997-07-14 (Date of the original deposit)¹.</p>	
IV. RECEIPT OF REQUEST FOR CONVERSION	
<p>The microorganism identified under I above was received by this International Depositary Authority on (date of original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion).</p>	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s)  Date: 1997-07-15


¹ Where Rule 6.4 (d) applies, such date is the date on which the status of international depositary authority was acquired.

Novartis AG

CH-4002 Basel

VIABILITY STATEMENT

issued pursuant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: Novartis AG Address: CH-4002 Basel	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM 11655 Date of the deposit or the transfer ¹ : 1997-07-14
III. VIABILITY STATEMENT	
The viability of the microorganism identified under II above was tested on 1997-07-14 ¹ . On that date, the said microorganism was (X) ² viable () ² no longer viable	
IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED ⁴	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s):  Date: 1997-07-15

¹ Indicate the date of original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).

² In the cases referred to in Rule 10.2(a) (ii) and (iii), refer to the most recent viability test.

³ Mark with a cross the applicable box.

⁴ Fill in if the information has been requested and if the results of the test were negative.

Novartis AG

CH-4002 Basel

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM	
Identification reference given by the DEPOSITOR: pNE95	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM 11656
II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION	
<p>The microorganism identified under I. above was accompanied by:</p> <p>(X) a scientific description (X) a proposed taxonomic designation</p> <p>(Mark with a cross where applicable).</p>	
III. RECEIPT AND ACCEPTANCE	
<p>This International Depositary Authority accepts the microorganism identified under I. above, which was received by it on 1997-07-14 (Date of the original deposit)¹.</p>	
IV. RECEIPT OF REQUEST FOR CONVERSION	
<p>The microorganism identified under I above was received by this International Depositary Authority on (date of original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion).</p>	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): <i>U. Wechs</i> Date: 1997-07-15

¹ Where Rule 6.4 (d) applies, such date is the date on which the status of international depositary authority was acquired.

Novartis AG

CH-4002 Basel

VIABILITY STATEMENT

issued pursuant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: Novartis AG Address: CH-4002 Basel	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM 11656 Date of the deposit or the transfer ¹ : 1997-07-14
III. VIABILITY STATEMENT	
The viability of the microorganism identified under II above was tested on 1997-07-14 ² . On that date, the said microorganism was (X) ³ viable () ³ no longer viable	
IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED ⁴	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): <i>V. Wechs</i> Date: 1997-07-15,

¹ Indicate the date of original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).

² In the cases referred to in Rule 10.2(a) (ii) and (iii), refer to the most recent viability test.


³ Mark with a cross the applicable box.

⁴ Fill in if the information has been requested and if the results of the test were negative.

Novartis AG

CH-4002 Basel

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM	
Identification reference given by the DEPOSITOR: pNE112	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM 11657
II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION	
The microorganism identified under I. above was accompanied by: <input checked="" type="checkbox"/> a scientific description <input checked="" type="checkbox"/> a proposed taxonomic designation (Mark with a cross where applicable).	
III. RECEIPT AND ACCEPTANCE	
This International Depositary Authority accepts the microorganism identified under I. above, which was received by it on 1997-07-14 (Date of the original deposit) ¹ .	
IV. RECEIPT OF REQUEST FOR CONVERSION	
The microorganism identified under I above was received by this International Depositary Authority on (date of original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion).	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s):  Date: 1997-07-15


¹ Where Rule 6.4 (d) applies, such date is the date on which the status of international depositary authority was acquired.

Novartis AG

CH-4002 Basel

VIABILITY STATEMENT

issued pursuant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: Novartis AG Address: CH-4002 Basel	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM 11657 Date of the deposit or the transfer ¹ : 1997-07-14
III. VIABILITY STATEMENT	
The viability of the microorganism identified under II above was tested on 1997-07-14 ¹ . On that date, the said microorganism was <input checked="" type="checkbox"/> viable <input type="checkbox"/> no longer viable	
IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED ⁴	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s):  Date: 1997-07-15

- ¹ Indicate the date of original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).
² In the cases referred to in Rule 10.2(a) (ii) and (iii), refer to the most recent viability test.
³ Mark with a cross the applicable box.
⁴ Fill in if the information has been requested and if the results of the test were negative.

What is claimed is:

1. A DNA fragment from the genome of *Amycolatopsis mediterranei* which comprises a DNA region which is involved directly or indirectly in the gene cluster responsible for rifamycin synthesis, including the adjacent DNA regions to the right and left which, by reason of their function in connection with rifamycin biosynthesis, qualify as constituent of this rifamycin gene cluster; and functional fragments, derivatives or constituents thereof.
2. A DNA fragment according to claim 1, which is directly or indirectly involved in the gene cluster responsible for rifamycin synthesis.
3. A DNA fragment according to claim 1, which comprises sequence portions which code for a polyketide synthase or an enzymatically active domain thereof.
4. A DNA fragment according to claim 1, which comprises SEQ ID NO 1 or SEQ ID NO 3 or at least 15 consecutive nucleotides therefrom.
5. A DNA fragment according to claim 1, wherein said fragment comprises one or more of the partial nucleotide sequences depicted in SEQ ID NOS 1 and/or 3, or functional fragments thereof, and all other DNA sequences in the vicinity of this sequence which can, by reason of homologies which are present, be regarded as structural or functional equivalents and are therefore able to hybridize with this sequence.
6. A DNA fragment according to claim 1, wherein said fragment comprises a nucleotide sequence selected from the group consisting of ORF A, B, C, D, E and F or functional fragments thereof, or encodes one or more of the proteins or polypeptides, or functional derivatives thereof, depicted in SEQ ID NOS 4 to 9.
7. A method for identifying, isolating and cloning a DNA fragment according to claim 1.

8. A method according to claim 7, which comprises the following steps:
 - setting up of a genomic gene bank,
 - screening of this gene bank with the assistance of the DNA sequences according to the invention, and
 - isolation of the clones identified as positive.
9. The use of a DNA fragment according to claim 1 in the production of ansamycins or precursors thereof; including those in which the aliphatic bridge is connected only at one end to the aromatic nucleus.
10. The use of a DNA fragment according to claim 1 in the production of rifamycin, rifamycin analogues or precursors thereof.
11. The use of a DNA fragment according to claim 1 for inactivating or modifying genes of ansamycin biosynthesis.
12. The use of a DNA fragment according to claim 1 for inactivating or modifying genes of rifamycin biosynthesis, or the biosynthesis of rifamycin analogues.
13. The use of a DNA fragment according to claim 1 for constructing mutated actinomycetes strains from which the natural rifamycin or ansamycin biosynthesis gene cluster in the chromosome has been partly or completely deleted.
14. The use of DNA fragments according to claim 1 for assembling a library of polyketide synthases.
15. The use of the polyketide synthases according to claim 14 for assembling a library of polyketides.
16. A polyketide synthase from *Amycolatopsis mediterranei* which is directly or indirectly involved in rifamycin synthesis; and functional constituents or domains thereof.

17. The use of the polyketide synthase according to claim 16 for synthesizing ansamycins.
18. The use of polyketide synthases according to claim 14 for synthesizing a library of ansamycins.
19. A hybrid vector comprising a DNA fragment according to claim 1.
20. A hybrid vector comprising an expression vector comprising a DNA fragment according to claim 1.
21. A host organism comprising a hybrid vector according to claim 19.
22. A hybridization probe comprising a DNA fragment according to claim 1.
23. The use of the hybridization probe according to claim 22 for identifying DNA fragments involved in the biosynthesis of ansamycins.

INTERNATIONAL SEARCH REPORT

In national Application No

PCT/EP 97/04495

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/52 C12P17/18 C12P17/10 C12N9/00 C12N1/21
C12N15/70 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LAL, R. ET AL: "Rifamycins: strain improvement program" CRIT. REV. MICROBIOL. (1995), 21(1), 19-30 CODEN: CRVMAC; ISSN: 1040-841X, XP000615990 see the whole document ---	1
Y	MADON J ET AL: "TRANSFORMATION SYSTEM FOR AMYCOLATOPSIS -MEDITERRANEI DIRECT TRANSFORMATION OF MYCELIUM WITH PLASMID DNA." J BACTERIOL 173 (20). 1991. 6325-6331. CODEN: JOBAAY ISSN: 0021-9193, XP000615993 see the whole document ---	1
A	WO 87 03907 A (LUBRIZOL GENETICS INC) 2 July 1987 see claims --- -/--	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search 7 January 1998	Date of mailing of the international search report 13/01/1998
Name and mailing address of the ISA European Patent Office P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Authorized officer Delanghe, L

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/04495

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 95 08548 A (UNIV LELAND STANFORD JUNIOR ;JOHN INNES CENTRE (GB)) 30 March 1995 see claims</p> <p style="text-align: center;">-----</p>	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 97/04495

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		AU 6835487 A	15-07-87
		EP 0262154 A	06-04-88
		EP 0463707 A	02-01-92

WO 9508548 A	30-03-95	US 5672491 A	30-09-97
		AU 678058 B	15-05-97
		AU 7731794 A	10-04-95
		CA 2171629 A	30-03-95
		EP 0725778 A	14-08-96
		JP 9505983 T	17-06-97
